(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
29 August 2002 (29.08.2002)

PCT

(10) International Publication Number
WO 02/066477 A2

(51) International Patent Classification[7]: C07D 471/04, A61K 31/437, A61P 5/00, 5/00 // (C07D 471/04, 235:00, 221:00)

(21) International Application Number: PCT/GB02/00634

(22) International Filing Date: 15 February 2002 (15.02.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0100567-7 20 February 2001 (20.02.2001) SE

(71) Applicant *(for AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, SZ, BE, CY, FR, GR, IE, IT, MC, NL, BF only)*: **ASTRAZENECA AB** [SE/SE]; Sodertalje, S- 151 85 (SE).

(71) Applicant *(for MG only)*: **ASTRAZENECA UK LIMITED** [GB/GB]; 15 Stanhope Gate, London, Greater London W1Y 6LN (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **DOSSETTER, Alexander, Graham** [GB/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). **KENNY, Peter** [GB/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). **MCKERRECHER, Darren** [GB/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). **WARDLEWORTH, Michael** [GB/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).

(74) Agent: **BRYANT, Tracey, et al**; Astrazeneca, Global Intellectual Property, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

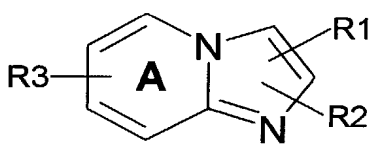
Declaration under Rule 4.17:
— *of inventorship (Rule 4.17(iv)) for US only*

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/066477 A2

(54) Title: COMPOUNDS



(I)

(57) Abstract: The present invention relates to compounds of formula I which are antagonists of gonadotropin releasing hormone (GnRH) activity. The invention also relates to pharmaceutical formulations, the use of a compound of the present invention in the manufacture of a medicament, a method of therapeutic treatment using such a compound and processes for producing the compounds wherein: - R1, R2 and R3 are as defined in the description; and ring A is optionally further substituted.

COMPOUNDS

The present invention relates to compounds which are antagonists of gonadotropin releasing hormone (GnRH) activity. The invention also relates to pharmaceutical formulations, the use of a compound of the present invention in the manufacture of a medicament, a method of therapeutic treatment using such a compound and processes for producing the compounds.

BACKGROUND TO THE INVENTION

Gonadotropin releasing hormone (GnRH) is a decapeptide that is secreted by the hypothalamus into the hypophyseal portal circulation in response to neural and/or chemical stimuli, causing the biosynthesis and release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) by the pituitary. GnRH is also known by other names, including gonadoliberin, LH releasing hormone (LHRH), FSH releasing hormone (FSH RH) and LH/FSH releasing factor (LH/FSH RF).

GnRH plays an important role in regulating the action of LH and FSH (by regulation of their levels), and thus has a role in regulating the levels of gonadal steroids in both sexes, including the sex hormones progesterone, oestrogens and androgens. More discussion of GnRH can be found in WO 98/5519 and WO 97/14697, the disclosures of which are incorporated herein by reference.

It is believed that several diseases would benefit from the regulation of GnRH activity, in particular by antagonising such activity. These include sex hormone related conditions such as sex hormone dependent cancer, benign prostatic hypertrophy and myoma of the uterus. Examples of sex hormone dependent cancers are prostatic cancer, uterine cancer, breast cancer and pituitary gonadotrophe adenoma.

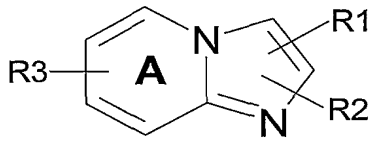
The following disclose compounds purported to act as GnRH antagonists: WO 97/44041, WO 98/5519, WO 99/51596 and WO 97/14697.

It would be desirable to provide further compounds, such compounds being GnRH antagonists.

SUMMARY OF THE INVENTION

The present invention accordingly provides a compound of formula **I** or a pharmaceutically acceptable salt or solvate thereof

I



wherein:-

R1, R2 and R3 are independently selected from hydrogen and a group bonded through a carbon atom, a nitrogen atom, an oxygen atom or a sulphur atom; and ring **A** is optionally further substituted.

The present invention also provides a pharmaceutical formulation comprising such a compound and a pharmaceutically acceptable diluent or carrier.

Furthermore, the present invention provides the following uses of the compound:-

(a) Use in the manufacture of a composition, for antagonising gonadotropin releasing hormone activity.

(b) Use in the manufacture of a medicament for administration to a patient, for reducing the secretion of luteinising hormone by the pituitary gland of the patient.

(c) Use in the manufacture of a medicament for administration to a patient, for therapeutically treating and/or preventing a sex hormone related condition in the patient.

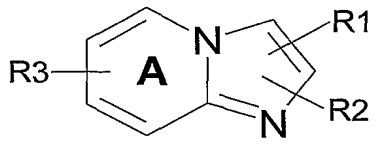
The present invention also relates to a method of antagonising gonadotropin releasing hormone activity in a patient, comprising administering the compound to the patient.

In addition, the invention provides a process of producing the compound.

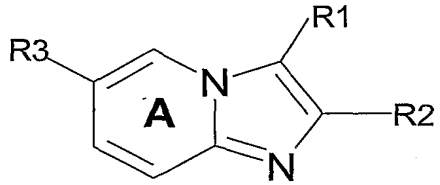
DETAILED DESCRIPTION OF THE INVENTION

As discussed above, the present invention provides a compound of formula **I** or **II** or a pharmaceutically acceptable salt or solvate thereof

I



II



wherein:-

R1, R2 and R3 are independently selected from hydrogen and a group bonded through a carbon atom, a nitrogen atom, an oxygen atom or a sulphur atom; and ring

A is optionally further substituted.

For definitions of preferred R1, R2 and R3 substituents, reference is made to WO 97/14697, where the definition of R^1 and R^2 in WO 97/14697 correspond with R1 and R2 respectively of the present invention, and the definition of R^4 or R^5 corresponds with R3 of the present invention. This disclosure of WO 97/14697, which provides disclosure of preferred R1, R2 and R3 substituents of the present invention, is explicitly incorporated herein by reference.

For further definitions of preferred R1, R2 and R3 substituents, reference is made to WO 95/28405, where the definition of R^1 and R^2 in WO 95/28405 correspond with R1 and R2 respectively of the present invention, and the definition of R^4 or R^5 corresponds with R3 of the present invention. This disclosure of WO 95/28405, which provides disclosure of preferred R1, R2 and R3 substituents of the present invention, is explicitly incorporated herein by reference.

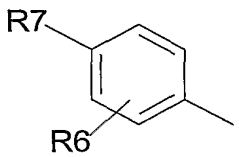
For yet further definitions of preferred R1, R2 and R3 substituents, reference is made to WO 97/40846, where the definition of R^{1a} and R^{2a} in WO 97/40846 correspond with R1 and R2 respectively of the present invention, and the definition of R^{3a}, R^{4a}, R^{5a} or R^{6a} corresponds with R3 of the present invention. In addition, the definition of R^{1e} and R^{2e} in WO 97/40846 correspond with R1 and R2 respectively of the present invention, and the definition of R^{3e}, R^{4e}, R^{5e} or R^{6e} corresponds with R3 of the present invention. This disclosure of WO 97/40846, which provides disclosure of preferred R1, R2 and R3 substituents of the present invention, is explicitly incorporated herein by reference.

Preferably, R1 and R2 are independently selected from a group of the formula R8-$(CH_2)_b$-, wherein each b independently represents zero or an integer from 1 to 5 and each R8 represents a group bonded through a nitrogen atom; a group of of the formula R9-B'-, wherein R9 is an optionally substituted phenyl and B' is a chemical bond or spacer group; R10-$(CH_2)_c$-, wherein R10 is an optionally substituted amino and c is zero or an integer

from 1 to 5; an optionally substituted C6 to C14 aryl; an optionally substituted C1 to C20 hydrocarbon residue; and optionally substituted C1 to C6 alkyl. Alternative embodiments, having different R1 and R2 definitions are presented below.

Preferably, R3 is selected from $(CH_2)_a$-R4, wherein R4 represents an optionally substituted C6 to C14 aryl (eg, phenyl) or an optionally substituted homo- or bi-cyclic heterocyclic ring (eg, a 5- or 6-membered mono-cyclic ring) and a represents zero or an integer from 1 to 5 (preferably, 1 or 2); a group bonded through a heteroatom (eg, where the heteroatom is O, N or S); an optionally substituted C1 to C20 hydrocarbon residue (eg, optionally substituted C1 to C6 alkyl or C2 to C12 alkenyl); optionally substituted C1 to C6 alkyl; C1 to C6 alkyl substituted with a group bonded through a sulphur atom; OR5, wherein R5 represents H or C1 to C6 alkyl; a carbonyl group optionally substituted with a hydrocarbon residue, the residue being optionally substituted; an esterified or amidated carboxyl group; hydrogen; optionally substituted aralkyl; optionally substituted cycloalkyl; and a group of formula W-$(CH_2)_d$, wherein d represents zero or an integer from 1 to 5 and W represents aryl having an optional substitutent selected from halogen, nitro, cyano, amino, an optionally substituted carboxyl, alkylenedioxy wherein the alkylene is C1 to C6, and a group of formula –X-R', wherein X represents a chemical bond or a spacer group and R' represents an optionally substituted cycloalkyl or an optionally substituted heterocyclic group. Alternative embodiments, having different R3 definitions are presented below.

Preferably, R4 represents a group of the formula:-



wherein:-

R6 is selected from hydrogen; halogen; and a group bonded through a carbon atom, a nitrogen atom, an oxygen atom or a sulphur atom; and
R7 is selected from hydrogen; halogen; nitro; cyano; and a hydrocarbon residue optionally substituted by a group bonded through an oxygen atom, a nitrogen atom or a sulphur atom.

In an alternative preferred embodiment, R3 represents hydrogen; optionally substituted C1 to C6 alkyl; optionally substituted aryl; C1 to C3 perfluoroalkyl; CN; NO_2; halogen; or $R11O(CH_2)_e$ -;
wherein R11 represents hydrogen; optionally substituted C1 to C6 alkyl; optionally substituted aryl; optionally substituted aralkyl; an optionally substituted carbocyclic ring of 3-7 atoms; or a mono- or bi-cyclic heterocyclic ring comprising from 1 to 4 heteroatoms selected from O, N and S and being optionally substituted by R12, R13 and R14, or being optionally substituted by C1 to C6 alkyl substituted by a mono- or bi-cyclic heterocyclic ring comprising from 1 to 4 heteroatoms selected from O, N and S and which ring is optionally substituted by R12, R13 and R14;

For R12, R13 and R14, either:-

(a) R12, R13 and R14 independently represent hydrogen; optionally substituted C1 to C6 alkyl; optionally substituted C2 to C6 alkenyl; CN; nitro; C1 to C3 perfluoroalkyl; C1 to C3 perfluoroalkoxy; optionally substituted aryl; optionally substituted aralkyl; $(CH_2)_fS(O)_gR15$; or halogen; or

(b) R12 meets the definition in (a) and R13 and R14 together represent a 3C to 7C carbocyclic ring or a heterocyclic ring comprising from 1 to 3 heteroatoms selected from O, N and S;

R15 represents hydrogen; optionally substituted C1 to C6 alkyl; C1 to C3 perfluoroalkyl; or optionally substituted aryl;

e and f independently represent 0, 1, 2, 3, 4 or 5; and
g represents 0, 1 or 2.

In this alternative embodiment, for definitions of preferred R3 substituents, reference is made to WO 98/55119 or WO 99/41251, where the definition of R6 corresponds with R3 in this alternative embodiment of the present invention. These disclosures of WO 98/55119 and WO 99/41251, which provide disclosure of preferred R3 substituents, are explicitly incorporated herein by reference.

In this alternative embodiment, preferably ring **A** has a further substituent selected from halogen and –Q(R16)R17, wherein:-
Q represents N; O; $S(O)_h$; C(O); $(CR18R19)_i$; a single bond to R16; optionally substituted C2 to C6 alkenyl; or optionally substituted C2 to C6 alkynyl; with the proviso that when Q is O; $S(O)_h$; C(O); $(CR18R19)_i$; or a single bond, R17 is absent; and

For R16 and R17, either:-

(c) R16 represents hydrogen or optionally substituted C1 to C6 alkyl; and
R17 represents hydrogen; C(O)NR18R19; C(O)R20; NR18R19; C(O)R18; NR19C(O)R18; NR19C(O)NR18R19; $NR19S(O)_2R18$; $NR19S(O)_2NR18R19$; OC(O)R18; OC(O)NR18R19; OR18; $S(O)_jR18$; $S(O)_jNR18R19$; a mono- or bi-cyclic heterocyclic ring comprising from 1 to 4 heteroatoms selected from O, N and S and being optionally substituted by R21, R22 and R23, or being optionally substituted by an optionally substituted C1 to C6 alkyl; or

(d) the structure –Q(R16)R17 represents a heterocyclic ring comprising one or more heteroatoms selected from O, N and S and optionally substituted by R21, R22 and R23; or

(e) the structure –Q(R16)R17 represents a 3-7 membered carbocyclic ring or =O;

For R18 and R19, either:-

(f) Each R18 and R19 independently represents a bond; hydrogen; optionally substituted C1 to C6 alkyl; optionally substituted aryl; optionally substituted aralkyl; an optionally

substituted carbocyclic ring of 3-7 atoms; or a mono- or bi-cyclic heterocyclic ring comprising from 1 to 4 heteroatoms selected from O, N and S and being optionally substituted by R21, R22 and R23, or being optionally substituted by C1 to C6 alkyl substituted by a mono- or bi-cyclic heterocyclic ring comprising from 1 to 4 heteroatoms selected from O, N and S and which ring is optionally substituted by R21, R22 and R23; or

(g) R18 and R19 together form part of an optionally substituted 3 to 9-membered ring;

R20 represents hydrogen; optionally substituted C1 to C6 alkyl; optionally substituted aryl; or optionally substituted aralkyl;

For R21, R22 and R23, either:-

(h) Each R21, R22 and R23 independently represents hydrogen; optionally substituted C1 to C6 alkyl; optionally substituted C2 to C6 alkenyl; CN; nitro; C1 to C3 perfluoroalkyl; C1 to C3 perfluoroalkoxy; optionally substituted aryl; optionally substituted aralkyl; $R18O(CH_2)_k$, where R18 meets the definition in section (f); $(CH_2)_kS(O)_lR24$; or halogen; or

(i) R21 is as defined in section (h) and R22 and R23 together represent a C3 to C7 carbocyclic ring or a heterocyclic ring containing from 1 to 3 heteroatoms selected from O, N and S;

R24 represents hydrogen; optionally substituted C1 to C6 alkyl; C1 to C3 perfluoroalkyl; or optionally substituted aryl;

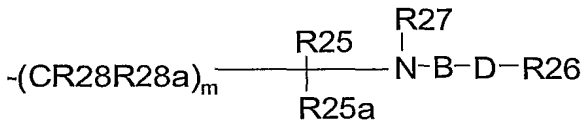
i and k independently represent 0, 1, 2, 3, 4 or 5; and

each h, j and l independently represent 0, 1 or 2.

In this embodiment, for definitions of a preferred further substituent of ring **A**, reference is made to WO 98/55119, WO 98/55123 or WO 99/41251, where the definition of –XR7(R8) corresponds with the further substituent of ring **A** in this alternative embodiment of the present invention. This disclosures of WO 98/55119, WO 98/55123 and WO 99/41251,

which provide disclosure of such a preferred further substituent, are explicitly incorporated herein by reference.

In an alternative embodiment, R1 represents the group



wherein:-

B represents R29-Y-R29, wherein Y represents optionally substituted aryl;

D is selected from a bond; -OR29-; -C(=O)R29-; -$S(O)_n$R29-; -NR29R30-; -OC(=O)R29-; -C(=O)OR29-; -NR31C(=O)R29-; -C(=O)NR31R29-; -$OS(O)_n$R29-; -$S(O)_n$OR29-; and –NR31$S(O)_n$R29-;

For R25, R25a, R27, R28 and R28a either:-

(i) R25, R25a, R27, R28 and R28a are independently selected from hydrogen; optionally substituted C1 to C6 alkyl; optionally substituted aryl; and optionally substituted aralkyl;

(j) R25 and R25a together represent a 3-7 membered carbocyclic ring or =O; and R27, R28 and R28a meet the definition in section (i);

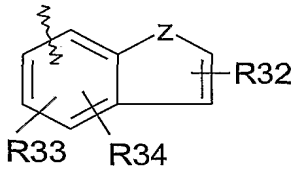
(k) R25, R25a and R27 meet the definition in section (i); and R28 and R28a together represent a 3-7 membered carbocyclic ring or =O;

(l) R25 and R28 together represent a heterocyclic ring comprising from 3 to 7 carbon atoms and at least one heteroatom; and R25a, R27 and R28a meet the definition in section (i);

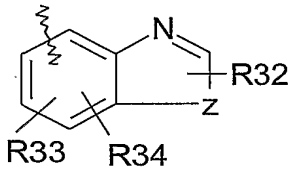
(m) R27 and R28 together represent a heterocyclic ring comprising from 3 to 7 carbon atoms and at least one heteroatom; and R25, R25a and R28a meet the definition in section (i); or

(n) R25 and R27 together represent a heterocyclic ring comprising from 3 to 7 carbon atoms and at least one heteroatom; and R25a, R28 and R28a meet the definition in section (i);

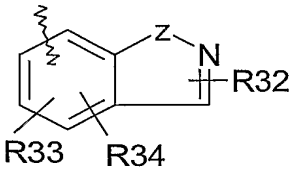
R26 represents a substituent selected from **III** to **XXIX** or an N-oxide thereof:-



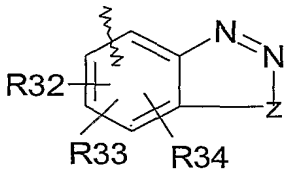
III



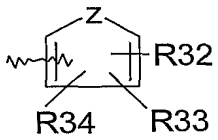
IV



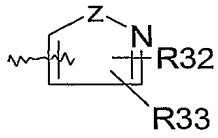
V



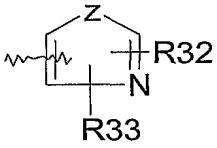
VI



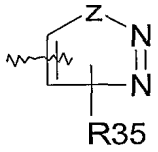
VII



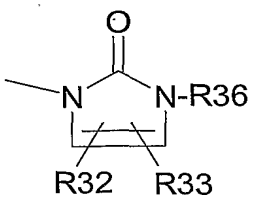
VIII



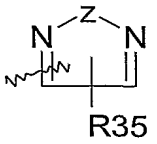
IX



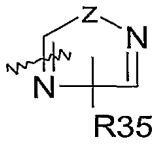
X



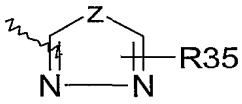
XI



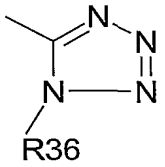
XII



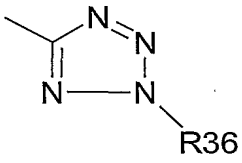
XIII



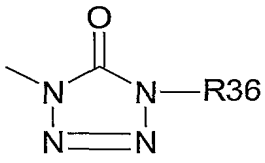
XIV



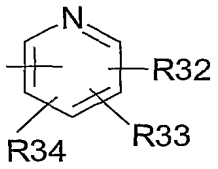
XV



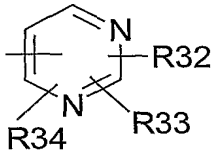
XVI



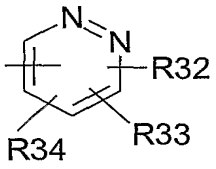
XVII



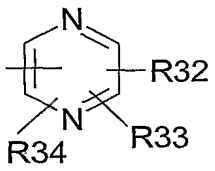
XVIII



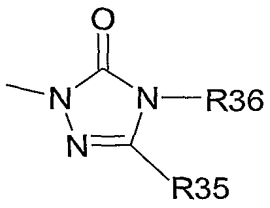
XIX



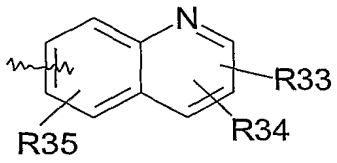
XX



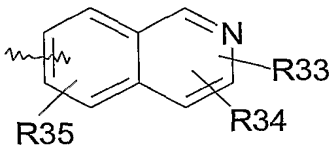
XXI



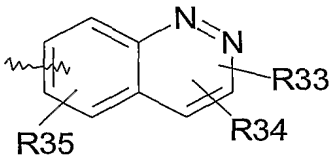
XXII



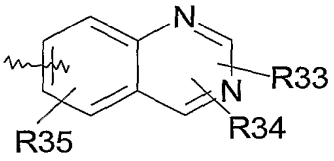
XXIII



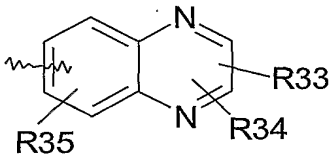
XXIV



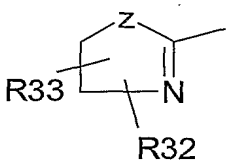
XXV



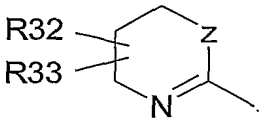
XXVI



XXVII



XXVIII



XXIX

Each R29 is independently selected from a bond and optionally substituted C1 to C4 alkyl;

R30 represents hydrogen; optionally substituted C1 to C6 alkyl; C(O)OR37; C(O)N(R37)$_2$; C(O)R37; or S(O)$_o$R37;

R31 and R36 independently represent hydrogen; optionally substituted C1 to C6 alkyl; optionally substituted aryl; optionally substituted aralkyl; an optionally substituted carbocyclic ring of 3-7 atoms; or a mono- or bi-cyclic heterocyclic ring comprising from 1 to 4 heteroatoms selected from O, N and S and being optionally substituted by R38, R39 and R40, or being optionally substituted by C1 to C6 alkyl substituted by a mono- or bi-cyclic heterocyclic ring comprising from 1 to 4 heteroatoms selected from O, N and S and which ring is optionally substituted by R38, R39 and R40;

R32 represents hydrogen; OH; NR41R42; NR37SO$_2$(optionally substituted C1 to C6 alkyl); NR37SO$_2$(optionally substituted aryl); NR37SO$_2$(C1 to C3 perfluoroalkyl); SO$_2$NR37(optionally substituted C1 to C6 alkyl); SO$_2$NR37(optionally substituted aryl); SO$_2$NR37(C1 to C3 perfluoroalkyl); SO$_2$NR37(C(O)-optionally substituted C1 to C6 alkyl); SO$_2$NR37(C(O)-optionally substituted aryl); S(O)$_p$(optionally substituted C1 to C6 alkyl); S(O)$_p$(optionally substituted aryl); C1 to C3 perfluoroalkyl; C1 to C3 perfluoroalkoxy; optionally substituted C1 to C6 alkoxy; COOH; halogen; NO$_2$; or CN;

R33 and R34 are independently selected from hydrogen; optionally substituted C1 to C6 alkyl; optionally substituted C2 to C6 alkenyl; CN; nitro; C1 to C3 perfluoroalkyl; C1 to C3 perfluoroalkoxy; optionally substituted aryl; optionally substituted aralkyl; R37O(CH$_2$)$_q$-; R37C(O)O(CH$_2$)$_q$-; R37OC(O)(CH$_2$)$_q$-; -(CH$_2$)$_q$S(O)$_r$R', where R' is hydrogen, optionally substituted C1 to C6 alkyl, C1 to C3 perfluoroalkyl or optionally substituted aryl; -(CH$_2$)$_q$C(O)N(R37)$_2$; or halogen;

R35 meets a definition of either R32 or R33;

Each R37 independently represents hydrogen; optionally substituted C1 to C6 alkyl; optionally substituted aryl; optionally substituted aralkyl; or an optionally substituted 3 to 7-membered carbocyclic ring;

R38, R39 and R40 independently represent hydrogen; optionally substituted C1 to C6 alkyl; optionally substituted C2 to C6 alkenyl; CN; nitro; C1 to C3 perfluoroalkyl; C1 to C3 perfluoroalkoxy; optionally substituted aryl; optionally substituted aralkyl; $(CH_2)_sS(O)_tR43$; or halogen;

For R41 and R42, either:-

(o) R41 represents hydrogen or optionally substituted C1 to C6 alkyl; and R42 represents hydrogen; C(O)NR18'R19'; C(O)R20'; NR18'R19'; C(O)R18'; NR19'C(O)R18'; NR19'C(O)NR18'R19'; NR19'$S(O)_2$R18'; NR19'$S(O)_2$NR18'R19'; OC(O)R18'; OC(O)NR18'R19'; OR18'; $S(O)_u$R18'; $S(O)_u$NR18'R19'; a mono- or bi-cyclic heterocyclic ring comprising from 1 to 4 heteroatoms selected from O, N and S and being optionally substituted by R21', R22' and R23', or being optionally substituted by an optionally substituted C1 to C6 alkyl; wherein R18', R19', R20', R21', R22' and R23' meet a definition respectively of R18, R19, R20, R21, R22 and R23 in claim 7; or

(p) the structure –N(R41)R42 represents a heterocyclic ring comprising one or more heteroatoms selected from O, N and S and optionally substituted by R21', R22' and R23'; wherein R21', R22' and R23' meet a definition respectively of R21, R22 and R23 in claim 7;

R43 represents hydrogen; optionally substituted C1 to C6 alkyl; C1 to C3 perfluoroalkyl; or optionally substituted aryl;

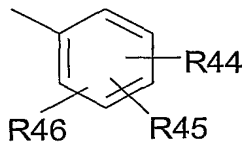
Z represents O, S or NR18';

R18' meets a definition of R18 in section (f) of claim 7;

Each m, q and s independently represent 0, 1, 2, 3, 4 or 5; and
n, o, p, r, t and u independently represent 0, 1 or 2.

In this alternative embodiment, for definitions of preferred R1 substituents, reference is made to WO 98/55119, WO 99/51231 or WO 99/41251, where the definition of $-(CR_9R_{9a})_m$-$CR_{10}(R_{10a})(NR_2((A)$-$(B)$-$R_1)$ or the definition of $-(CR_9R_{9a})_m$-$CR_{10}(R_{10a})(NR_2((A)$-$R_1)$ corresponds with R1 in this alternative embodiment of the present invention. These disclosures of WO 98/55119, WO 99/51231 and WO 99/41251, which provide disclosure of preferred R1 substituents, are explicitly incorporated herein by reference.

In an alternative embodiment, R2 represents represents a substituent of formula **XXX**:-



XXX

R44, R45 and R46 independently represent hydrogen; optionally substituted C1 to C6 alkyl; optionally substituted C2 to C6 alkenyl; CN; nitro; C1 to C3 perfluoroalkyl; C1 to C3 perfluoroalkoxy; optionally substituted aryl; optionally substituted aralkyl; $(CH_2)_vS(O)_wR47$; or halogen;

R47 represents hydrogen; optionally substituted C1 to C6 alkyl; C1 to C3 perfluoroalkyl; or optionally substituted aryl;

v represents 0, 1, 2, 3, 4 or 5; and

w represents 0, 1 or 2.

In this alternative embodiment, for definitions of preferred R2 substituents, reference is made to WO 98/55119, where the definition of the phenyl substituted by R3 to R5 in WO 98/55119 corresponds with R2 in this alternative embodiment of the present invention. This disclosure of WO 98/55119, which provides disclosure of preferred R2 substituents, is explicitly incorporated herein by reference.

In an alternative embodiment, R1 meets the definition of $-X-(A)-CR_9(R_{9a})-(B)-NR_{10}(R_{11})$ disclosed in WO 97/44037, WO 99/41251 or WO 97/44339, and these disclosures are explicitly incorporated herein by reference.

In an alternative embodiment, R2 meets the definition of Y disclosed in WO 97/44037 or the definition of the phenyl substituted by R_2, R_3 and R_4 given in the formula I disclosed in WO 97/44339 or WO 99/41251, and these disclosures are explicitly incorporated herein by reference.

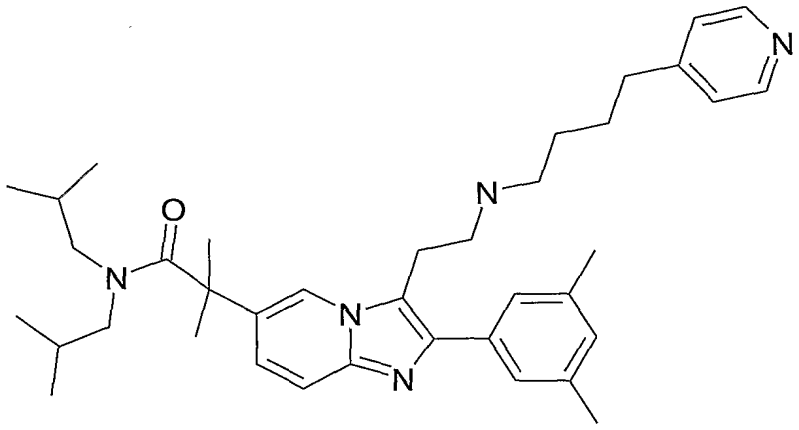
In an alternative embodiment, R3 meets a definition of R_5, R_6, R_7 or R_8 disclosed in WO 97/44037 or WO 97/44339, and ring **A** optionally has at least one further substituent meeting the definition of R_5, R_6, R_7 or R_8 disclosed in WO 97/44037 or WO 97/44339. The disclosure in WO 97/44037 and WO 97/44339 relating to R_5, R_6, R_7 or R_8 is explicitly incorporated herein by reference.

In the present specification, unless otherwise indicated, an alkyl, alkylene or alkenyl moiety (eg, the alkyl moiety of an alkylaryl substituent) may be linear or branched. Where C1 to C6 alkyl is mentioned, preferably this is C2 to C4 alkyl, and more preferably methyl. Where C2 to C6 alkenyl is mentioned, preferably this is C2 to C4 alkenyl, most preferably C2 or C3 alkenyl.

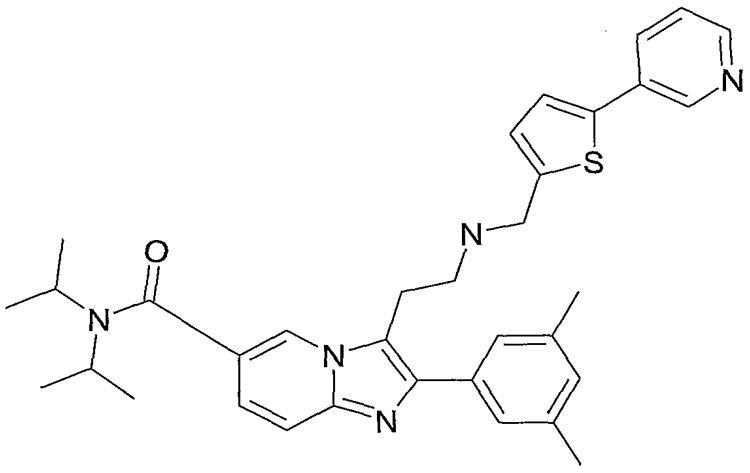
The term "alkylene" refers to $-CH_2-$. Thus, C8 alkylene for example is $-(CH_2)_8-$.

Where optional substitution is mentioned at various places above, this refers to one, two, three or more optional substituents. Unless otherwise indicated above (ie, where a list of optional substituents is provided), each substituent can be independently selected from C1 to C8 alkyl (preferably C2 to C6 alkyl, and most preferably methyl); O(C3 to C8 cycloalkyl), preferably O-cyclopropyl, or O-cyclobutyl or O-cyclopentyl; O(C1 to C6 alkyl), preferably Omethyl or O(C2 to C4 alkyl); halo, preferably Cl or F; $CHal_3$, $CHHal_2$, CH_2Hal, $OCHal_3$, $OCHHal_2$ or OCH_2Hal, wherein Hal represents halogen (preferably F); CH_2OR, NRCOR′, $NRSO_2R'$ or N-R-R′, wherein R and R′ independently represent H or C1 to C8 alkyl (preferably methyl or C2 to C6 alkyl or C2 to C4 alkyl) , or N-R-R′ represents an optionally substituted C3 to C8, preferably C3 to C6, heterocyclic ring optionally containing from 1 to 3 further heteroatoms independently selected from O, N and S; H; or COOR″ or COR″, R″ representing H, optionally substituted phenyl or C1 to C6 alkyl (preferably methyl, ethyl, *i*-propyl or *t*-butyl). For optional substitution of the heterocyclic ring represented by N-R-R′, at least one (eg, one, two or three) substituents may be provided independently selected from C1 to C6 alkyl (preferably C2 to C4 alkyl, more preferably methyl); phenyl; OCF_3; $OCHF_2$; -O(C1-C8 alkyl), preferably –O-methyl, -O-ethyl or –O(C3 to C6 alkyl); -C(O)O(C1-C8 alkyl), preferably –C(O)O-methyl, -C(O)O-ethyl, -C(O)O-*tert*-butyl or –C(O)O(C3 to C6 alkyl); -C(O)O-phenyl; -O-phenyl; -C(O) (C1-C8 alkyl), preferably –C(O)-methyl, -C(O)-ethyl or –C(O)(C3 to C6 alkyl) ; -C(O)OH; -S(C1-C8 alkyl), preferably –S-methyl, -S-ethyl or –S(C3 to C6 alkyl); OH; halogen (eg, F, Cl or Br), NRR' where R and R' are independently H or C1 to C6 alkyl (preferably C2 to C4 alkyl, more preferably methyl, most preferably R=R'=methyl); and nitro.

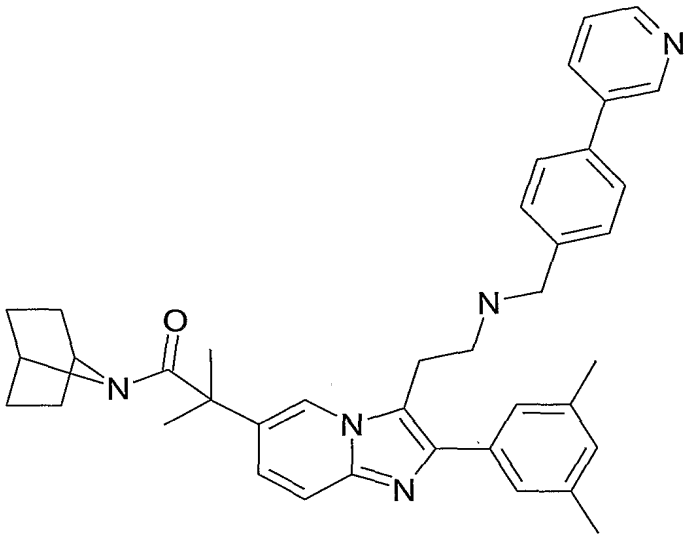
Particularly preferred compounds according to the present invention are:-



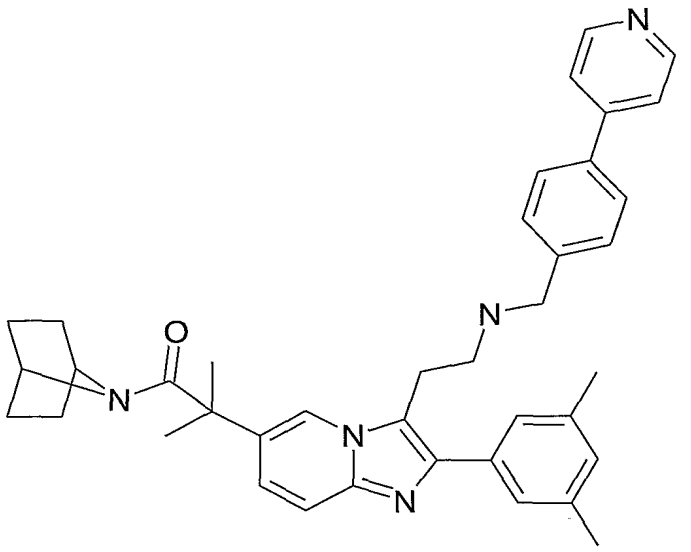
2-{2-(3,5-Dimethyl-phenyl)-3-[2-(4-pyridin-4-yl-butylamino)-ethyl]-imidazo[1,2-a]pyridin-6-yl}-N,N-diisobutyl-isobutyramide;



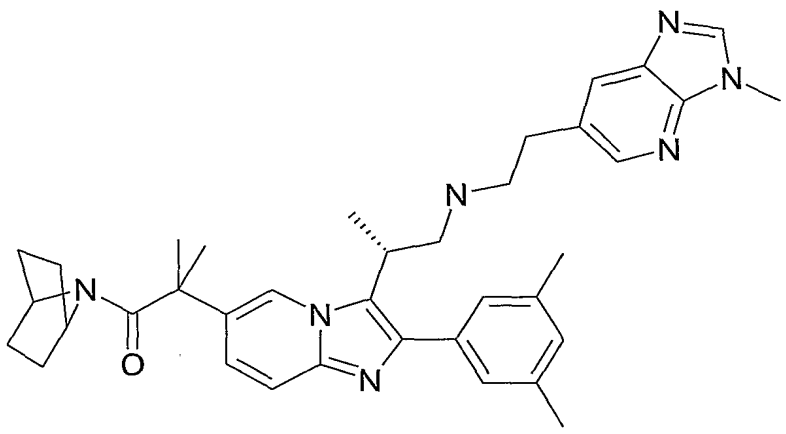
2-(3,5-Dimethyl-phenyl)-3-{2-[(5-pyridin-3-yl-thiophen-2-ylmethyl)-amino]-ethyl}-imidazo[1,2-a]pyridine-6-carboxylic acid diisopropylamide;



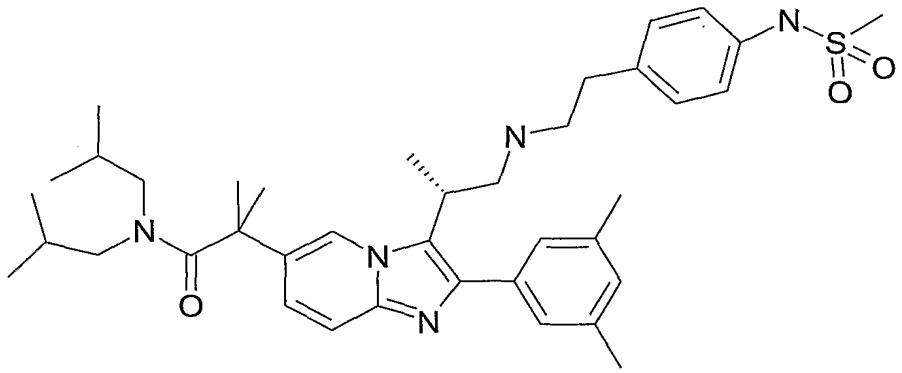
1-(7-Aza-bicyclo[2.2.1]hept-7-yl)-2-{2-(3,5-dimethyl-phenyl)-3-[2-(4-pyridin-3-yl-benzylamino)-ethyl]-imidazo[1,2-a]pyridin-6-yl}-2-methyl-propan-1-one;



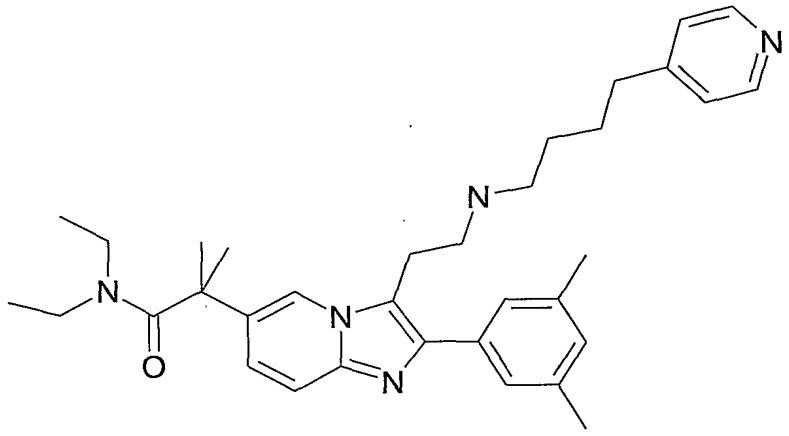
1-(7-Aza-bicyclo[2.2.1]hept-7-yl)-2-{2-(3,5-dimethyl-phenyl)-3-[2-(4-pyridin-4-yl-benzylamino)-ethyl]-imidazo[1,2-a]pyridin-6-yl}-2-methyl-propan-1-one;



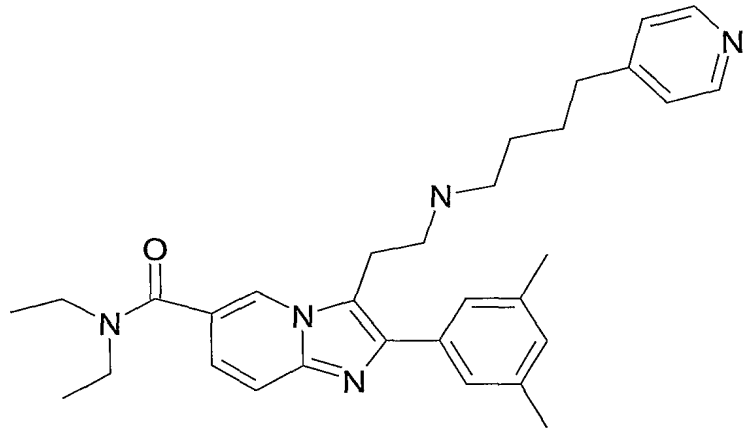
1-(7-Aza-bicylco[2.2.1]hept-7-yl)-2-(2-(3,5-dimethyl-phenyl)-3-{(R)-1-methyl-2-[2-(3-methyl-3*H*-imidazo[4,5-*b*]pyridin-6-yl)-ethylamino]-ethyl}-imidazo[1,2-*a*]pyridin-6-yl)-2-methyl-propan-1-one;



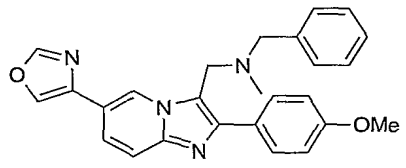
2-(2-(3,5-dimethyl-phenyl)-3-{(R)-2-[2-(4-methanesulfonylamino-phenyl)-ethylamino]-1-methyl-ethyl}-imidazo[1,2-*a*]pyridin-6-yl)-*N*,*N*-diisobutyl-isobutyramide;



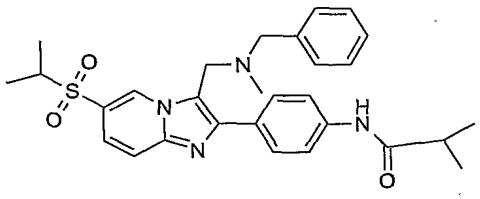
2-{2-(3,5-dimethyl-phenyl)-3-[2-(4-pyridin-4-yl-butylamino)-ethyl]-imidazo[1,2-*a*]pyridin-6-yl}-*N*,*N*-diethyl-isobutyramide;



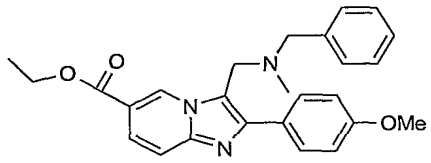
2-(3,5-dimethyl-phenyl)-3-[2-(4-pyridin-4-yl-butylamino)-ethyl]-imidazo[1,2-*a*]pyridine-6-carboxylic acid diethylamide;



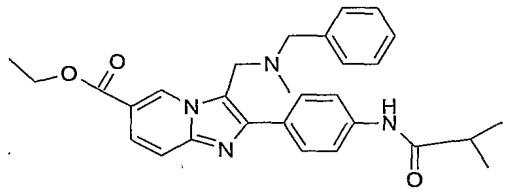
Benzyl-[2-(4-methoxyphenyl)-6-oxazol-4-yl-imidazo[1,2-a]pyridin-3-ylmethyl]-methylamine;



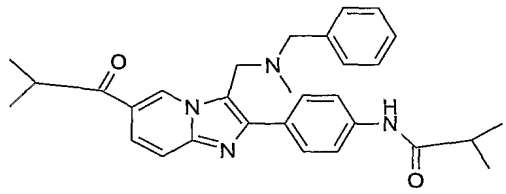
Propane-2-sulfonic acid 3-[(benzylmethylamino)-methyl]-2-[4-(2-methyl-propanoylamino)-phenyl]-imidazo[1,2-a]pyridin-6-yl ester;



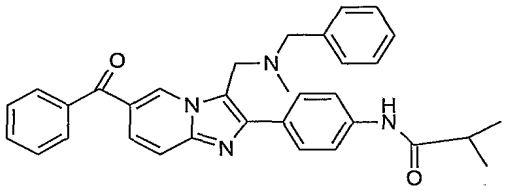
3-[(Benzylmethylamino)-methyl]-2-(4-methoxyphenyl)-imidazo[1,2-a]pyridine-6-carboxylic acid ethyl ester;



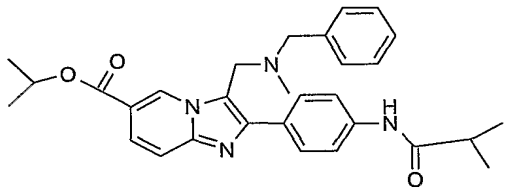
2-(4-Acetylaminophenyl)-3-[(benzylmethylamino)-methyl]-imidazo[1,2-a]pyridine-6-carboxylic acid ethyl ester;



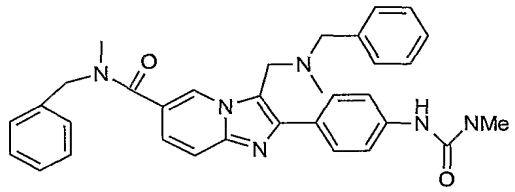
N-{4-[3-(Benzylmethylamino)-methyl]-6-(2-methylpropanoyl)-imidazo[1,2-a]pyridin-2-yl]-phenyl}-isobutyramide;



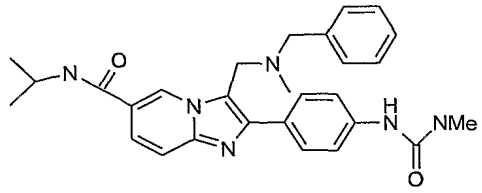
N-{4-[3-(Benzylmethylamino)-methyl]-6-(1-phenylmethanoyl)-imidazo[1,2-a]pyridin-2-yl]-phenyl}-isobutyramide;



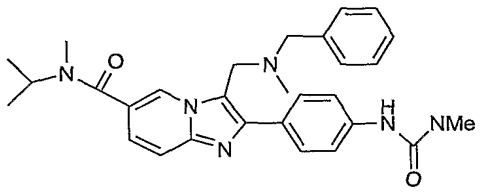
3-[(Benzylmethylamino)-methyl]-2-[4-(2-methyl-propanoylamino)-phenyl]-imidazo[1,2-a]pyridine-6-carboxylic acid isopropyl ester;



3-[(Benzylmethylamino)-methyl]-2-[4-(3-methylureido)-phenyl]-imidazo[1,2-a]pyridine-6-carboxylic acid benzylmethylamide;



3-[(Benzylmethylamino)-methyl]-2-[4-(3-methylureido)-phenyl]-imidazo[1,2-a]pyridine-6-carboxylic acid isopropylamide; and



3-[(Benzylmethylamino)-methyl]-2-[4-(3-methylureido)-phenyl]-imidazo[1,2-a]pyridine-6-carboxylic acid isopropylmethylamide.

The invention also contemplates pharmaceutically acceptable salts and solvates of these compounds and other compounds of formula **I** or **II**. Compounds of formula **I** or **II** may be converted to pharmaceutically acceptable salts and solvates thereof, preferably acid addition salts, such as hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartarate, citrate, oxalate, methanesulphonate or *p*-toluenesulphonate, or alkali metal salts such as sodium or potassium salts.

Full guidance is given below on processes for producing compounds according to the invention. It will be appreciated by those skilled in the art that in the processes of the present invention certain functional groups such as hydroxyl or amino groups in the starting reagents or intermediate compounds may need to be protected by protecting groups. Thus, the preparation of the compounds of formula **I** or **II** may involve, at an appropriate stage, the addition and subsequent removal of one or more protecting groups.

The protection and deprotection of functional groups is described in 'Protective Groups in Organic Chemistry', edited by J.W.F. McOmie, Plenum Press (1973) and 'Protective Groups in Organic Synthesis', 2nd edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (1991).

EXPERIMENTAL

The following reaction schemes and examples provide general guidance on how to produce compounds according to the invention. It will be apparent to the skilled addressee that the choice of reagents may need to be changed from those shown in order to produce a particlar compound according to the invention, and the skilled person can make a routine choice of reagents depending on the final compound to be synthesised. Further general guidance on producing compounds according to the present invention can be found in WO 98/55119, WO 99/51231, WO 97/44041, and WO 97/14697.

GENERAL REACTION SCHEMES

Definitions For Schemes

In the following schemes, the following definitions apply:-

For R1 and R2, either:-

(i) R1= -C(X)NR5R6; -C(=NCN)NR5R6; -C(=CHNO$_2$)NR5R6; an optionally substituted 5- to 10-membered mono- or bi-cyclic heterocyclic ring structure containing from 1 to 5 heteroatoms independently selected from O, N and S; optionally substituted C1 to C8 alkyl; optionally substituted aryl; or optionally substituted aralkyl, where the alkyl moiety is C1 to C8;

R2 = H; optionally substituted C1 to C8 alkyl; optionally substituted aryl; optionally substituted aralkyl; -R7-R8, wherein R7 represents optionally substituted C1 to C8 alkyl and R8 represents an optionally substituted 5- to 10-membered mono- or bi-cyclic heterocyclic ring structure containing from 1 to 5 heteroatoms independently selected from O, N and S; optionally substituted C2 to C12 alkenyl; or optionally substituted alkenylaryl, wherein the alkenyl moiety is C2 to C12; and

A = a single bond; optionally substituted C1 to C8 alkylene; a C2 to C12 group having at least one alkene double bond; or –R-Ar-R'-, where R and R' are independently selected from a bond, optionally substituted C1 to C8 alkylene and a C2 to C12 group having at least one alkene double bond; and Ar represents optionally substituted aryl; or

(ii) the structure N-R1R2 represents a 3- to 8- membered heterocyclic ring optionally containing from 1 to 3 further heteroatoms independently selected from O, N and S and optionally fused to a C5 to C10 ring structure, N-R1R2 being optionally substituted;

For R3 and R4, either R3 is selected from (iii) and R4 selected from (iv); or R3 is selected from (iv) and R4 selected from (iii):-

(iii) H; -ZR9, halogen; -ZC(O)NR9R10; -ZC(O)OR9; -ZC(O)SR9; -ZC(O)R9; C(R9)=N-OR10; -ZNR9C(O)NR10R11; -ZNR9SO_2R10; -ZSO_2R9R10; -ZCR9$(CN)_2$; -ZN(R9)CN; or an optionally substituted 3- to 6-membered heterocyclic ring containing from 1 to 3 heteroatoms independently selected from O, N and S;

(iv) -Z'-M, wherein

M represents a mono- or bi-cyclic aromatic ring structure optionally having at least one substituent selected from CN; NR12R13; an optionally substituted C1 to C8 alkyl; optionally substituted C1 to C8 alkoxy; halogen; $(CH_2)_b$-C(O)NR12R13; NR12-C(O)NR13R14; $(CH_2)_b$-SO_2NR12R13; NR12C(O)R13; NR12SO_2R13; $(CH_2)_b$OH; NR12CN; and CR12$(CN)_2$;

Wherein each R5, R6, R10, R11, R12, R13 and R14 is independently selected from H; optionally substituted C1 to C8 alkyl and optionally substituted aryl;

R9 is selected from H; optionally substituted C1 to C8 alkyl; optionally substituted aryl;

-R-Ar, where R represents C1 to C8 alkylene and Ar represents optionally substituted aryl; and optionally substituted 3- to 8- membered heterocyclic ring optionally containing from 1 to 3 further heteroatoms independently selected from O, N and S;

X = O; S; or NR''', where R''' is H or C1 to C8 alkyl;

Y = a bond; C1 to C8 alkylene; a C2 to C12 group having at least one alkene double bond; or a C2 to C12 group having at least one alkyne triple bond;

Z = a bond; C1 to C8 alkylene; a C2 to C12 group having at least one alkene double bond; a C2 to C12 group having at least one alkyne triple bond; or -CR(R'), where R and R' are independently selected from H, CN, halogen, C1 to C8 alkyl, CH_2F, CHF_2, and C3 to C8 cycloalkyl;

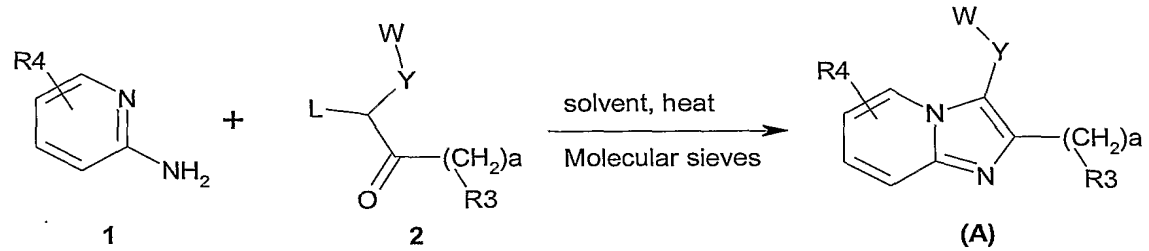
Z' = a bond; C1 to C8 alkylene; a C2 to C12 group having at least one alkene double bond; a C2 to C12 group having at least one alkyne triple bond; or -CR(R'), where R and R' are independently selected from H, CN, halogen, C1 to C8 alkyl, CH_2F, CHF_2, and C3 to C8 cycloalkyl;

a = zero or an integer from 1 to 8;

each b independently represents zero or an integer from 1 to 8;

Wherein ring **B** is optionally further substituted.

Schemes

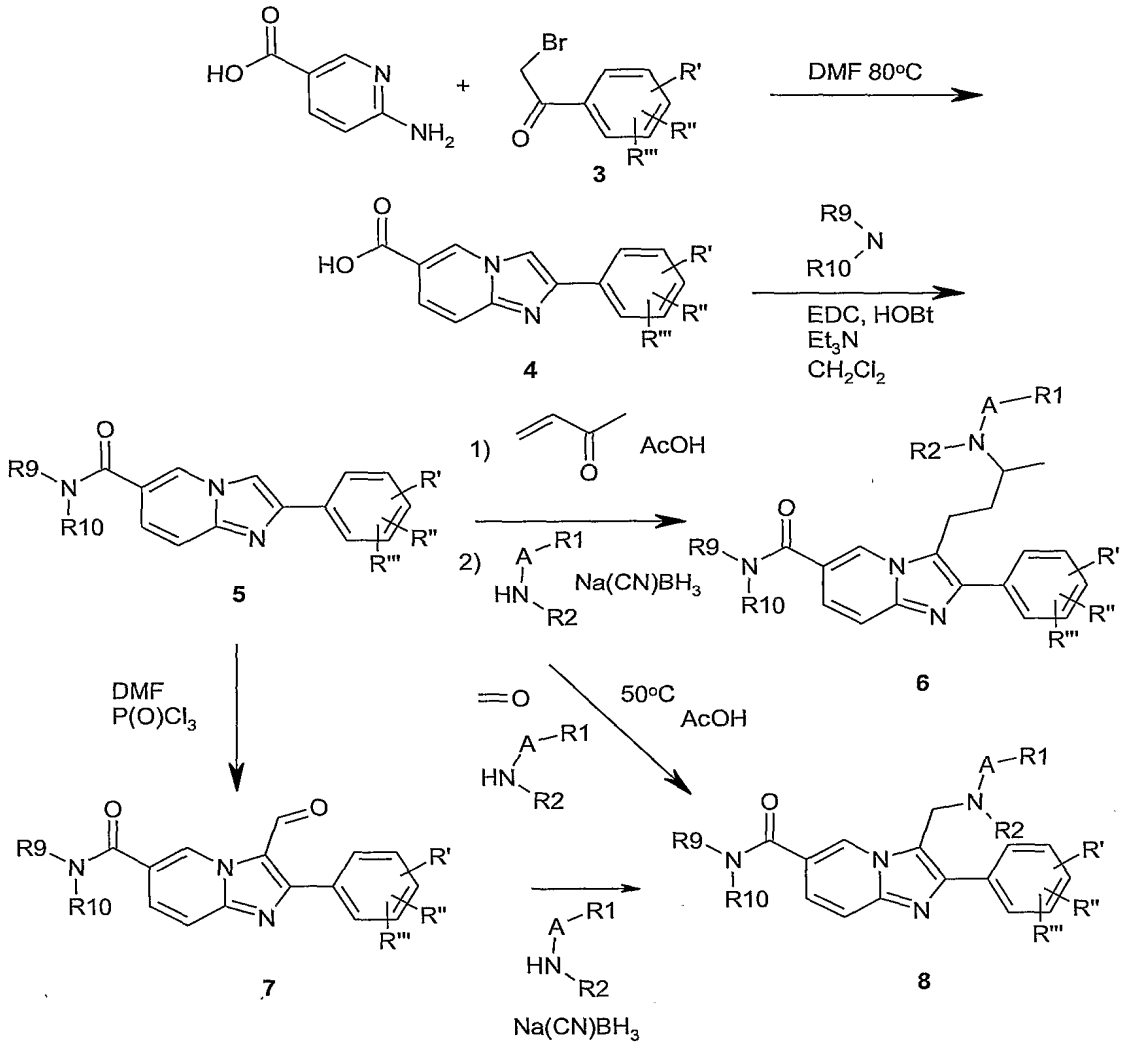


Scheme a

L=leaving group e.g. Cl, Br, I, OMesyl, OTosyl or H, W = epoxide or aziridines

W=group for elaboration into N(-(A)-R1)R2.

Imidazo[1,2-*a*]pyridines of the structure **(A)** can be prepared by the condensation of a suitable substituted 2-aminopyridine **1** and a ketone **2** bearing a leaving group α to the carbonyl group (Br preferred group). Heating at a temperature between 25 °C and 120 °C, preferably 80 °C, in a suitable solvent such as *N.N*-dimethylformamide (DMF), dimethylsulfoxide (DMSO), toluene, xylene, *t*-BuOH, preferable DMF, with or without the molecular sieves, for a period of 1 to 24 h, effects the condensation. With appropriately substituted groups (e.g. W), the amine group -N(-(A)-R1)R2 can then be installed by standard chemistry know to those skilled in the art which is detailed below.

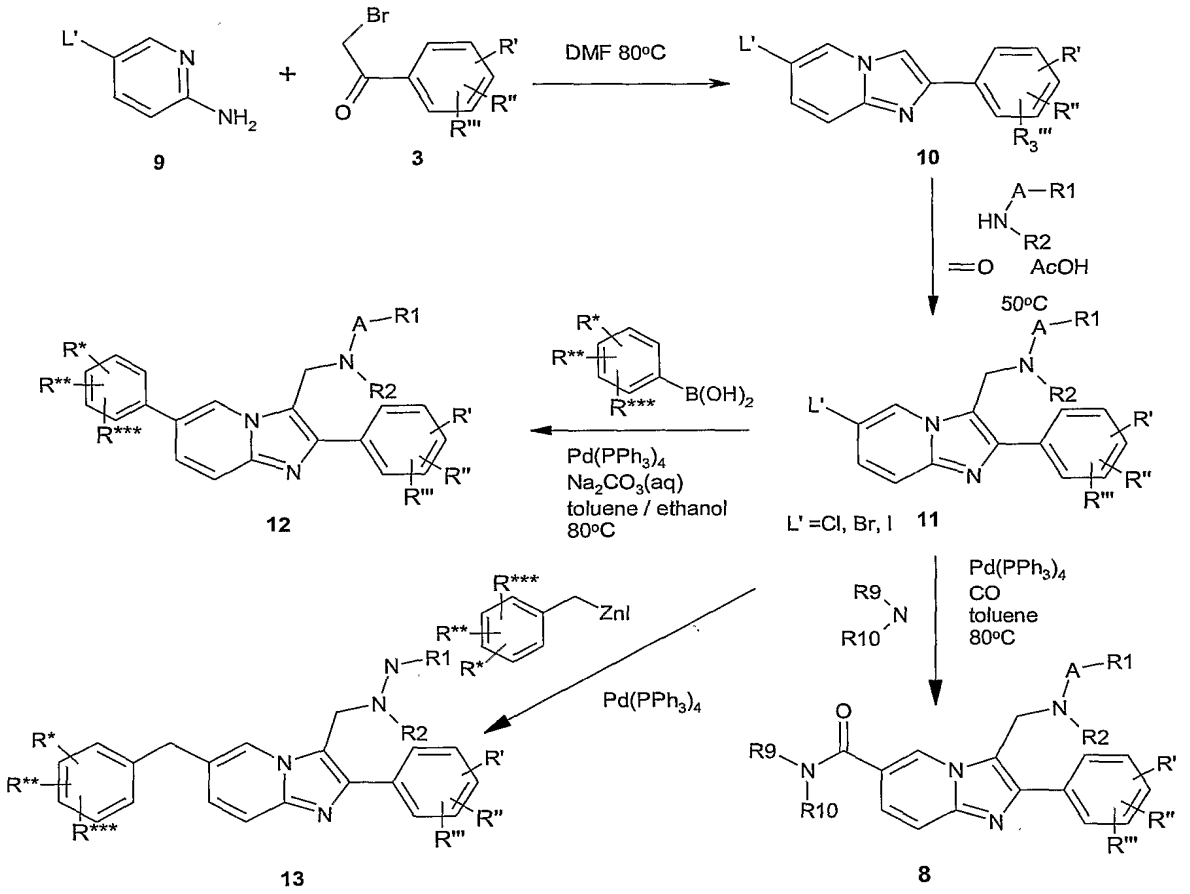


Scheme b

For example, Scheme b shows a general synthesis of 5-carbonyl-2-aryl-3-aminomethylimidazo[1,2-*a*]pyridine commencing with commercially available 2-aminopyridine and 2'-bromoacetophenone. Thus, condensation of 6-aminonicotinic acid and a 2'-bromoacetophenone **3,** under the preferred conditions noted above for the key cyclisation, yields the bicycle **4**. Condensation using the coupling reagent 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) or 1,3-dicyclohexylcarbodiimide (DCC) or the like, with or without 1-hydroxybenotriazole (HOBt) and suitable amine base, such as triethylamine and the like, in an inert solvent such as methylene chloride, chloroform, DMF, or mixtures thereof, at or near room temperature

for a period of 3 to 24h to provide the corresponding coupled product **5,** bearing the substituent N(R9)R10, where R9 and R10 are as defined above. Michael addition reactions can be achieved by the condensation of methyl vinyl ketone with the bicycle **5** by heating in an organic acid, such as acetic acid, to yield a ketone product. Reductive amination under typical conditions of an appropriately substituted amine and a hydride source, such as sodium cyanoborohydride, sodium borohyride, zinc borohyride, lithium borohydride and the like, yields products such as **6**. Using classical Mannich chemistry an aminomethyl group can be introduced by treatment of **5** with a mixture of a suitably substituted amine (NH(A-R1)(R2)) and paraformaldehyde. In an organic acid such as acetic acid and the like and stirring at room temperature or heating between 40 and 100°C in this manner compounds such as **8** which correspond to the general structure **(A)** where Y represents CH_2 are formed. Alternatively, a two step procedure may be employed, where a Vilsmeier reaction, classically employing DMF and phosphorus oxychloride at a temperature between -10 °C and 25 °C, installs a formyl group at the 3-position of the imidazo[1,2-a]pyridine to give **7**. Reduction amination employing a suitably substituted amine [HN(-(A)-R1)R2] and a reducing agent such as sodium borohydride, sodium cyanoborohydride, zinc borohydride and the such like, under acid or neutral conditions in a suitable solvent such as methylene chloride, chloroform, benzene, toluene and alcohols such as ethanol and the like, yields the 3-aminomethyl-imidazo[1,2-a]pyridines (**8**).

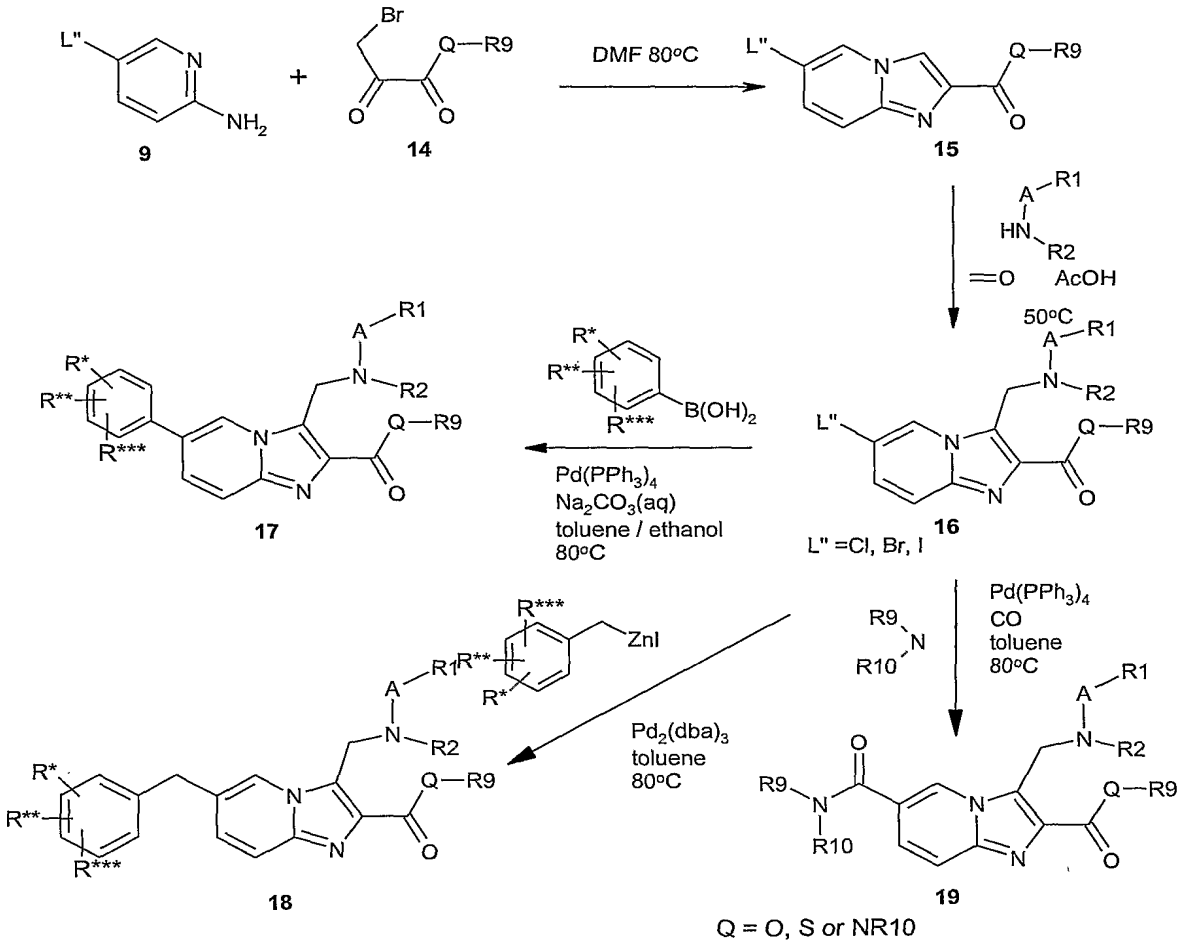
As an alternative to N(R9)R10, one can use R9OH in scheme b.



Scheme c

For example, Scheme c shows another general synthesis of 5-carbonyl-2-aryl-3-aminomethylimidazo[1,2-*a*]pyridine commencing with commercially available 2-aminopyridines and 2'-bromoacetophenone. Thus, condensation of 2-aminopyridine **9** and a 2'-bromoacetophenone **3** under the preferred conditions noted above for the key cyclisation yields the bicycle **10**. The Mannich reaction conditions described above for Scheme b again install the substituted aminomethyl group leading to the bicycle **11**. Where L' is chloride, bromide, iodide, O-trifluoromethanesulfonate, trialkyltin or like, **11** can be treated under palladium(0) catalysis with carbon monoxide at 1atm or higher pressure in the presence of a substituted amine (N(R9) R10 as shown), alcohol (R9OH – not shown) or thiol (R9SH – not shown) in an inert solvent such as toluene, benzene, dioxane, THF, DMF and the like to yield 5-carbonyl-2-aryl-3-aminomethylimidazo[1,2-*a*]pyridines such as **8**. Where L' is chloride, bromide, iodide, O-trifluoromethanesulfonate, trialkyltin or like **11** can be treated under palladium(0), a weak base such aqueous sodium carbonate and the

like and a substituted aryl boronic acid from commercial sources or prepared (as described in: Gronowitz, S.; Hornfeldt, A.-B.; Yang, Y.,-H *Chem. Sci.* **1986**, *26*, 311-314), in an inert solvent such as toluene, benzene, dioxane, THF, DMF and the like, with heating between 25 °C and 100 °C, preferably 80 °C, for a period of 1-12 hours, to give the imidazo[1,2-*a*]pyridine **12**. Similarly coupling of an arylalkylzinc iodide with **11** can be achieved using the methods of Negishi (e.g. Jackson, R. F. W.; James, H.; Wythes, M. J.; Wood, A. *J. Chem. Soc. Chem. Commun.* **1989**, 644) to yield imidazo[1,2-*a*]pyridines (**13**).

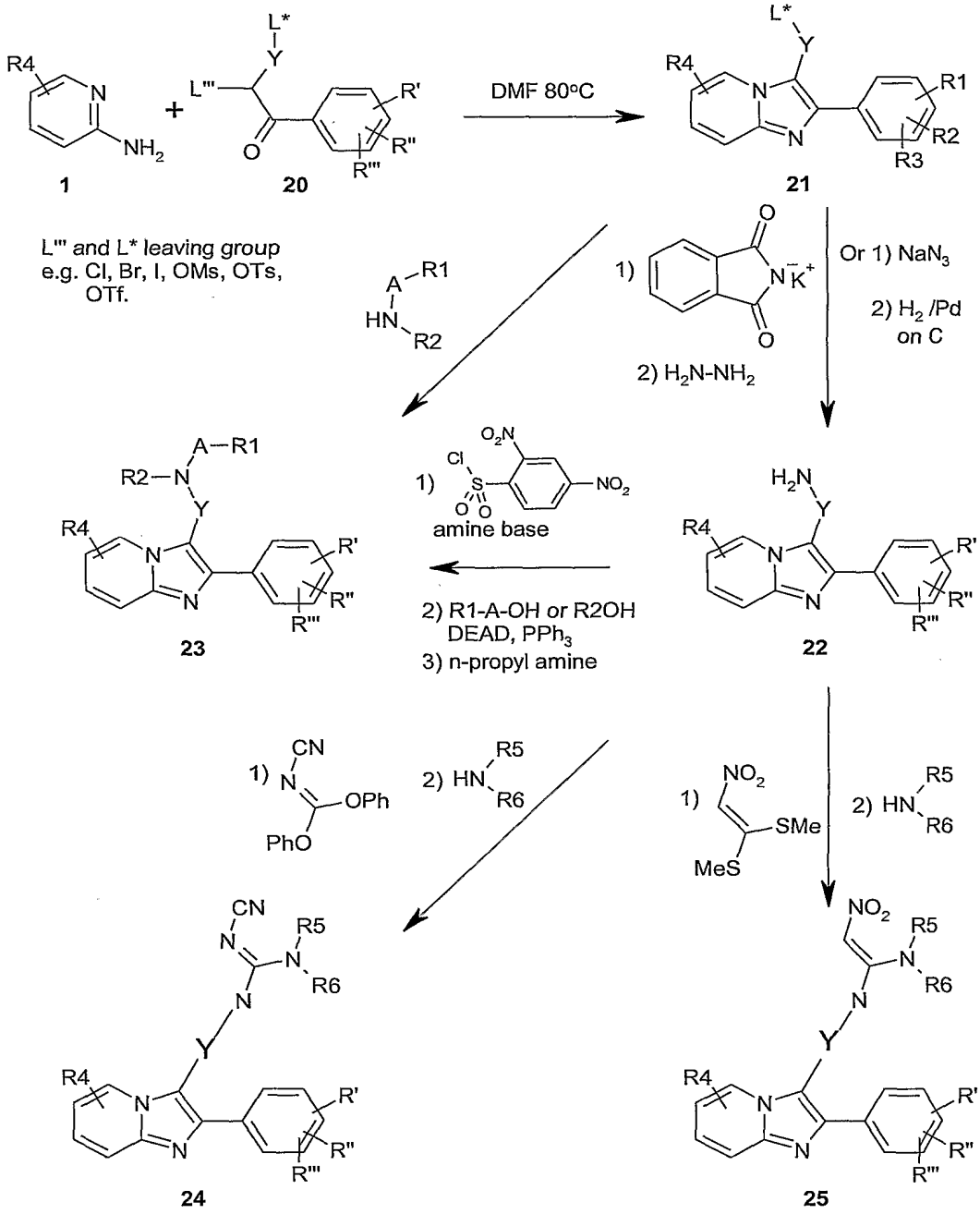


Scheme d

Condensation of a suitable substituted 2-aminopyridine **9** with a bromopyruvate **14** using the condition described above, yields 2-carboxyimidazo[1,2-*a*]pyridines **15**. With same chemical sequences of Mannich reaction then palladium catalysed carbonylation,

Suzuki couplings or Negishi couplings the 2-carboxyimidazo[1,2-*a*]pyrimidines **17**, **18** and **19** can be synthesised (Scheme d).

As an alternative to N(R9)R10, one can use R9OH in scheme d.

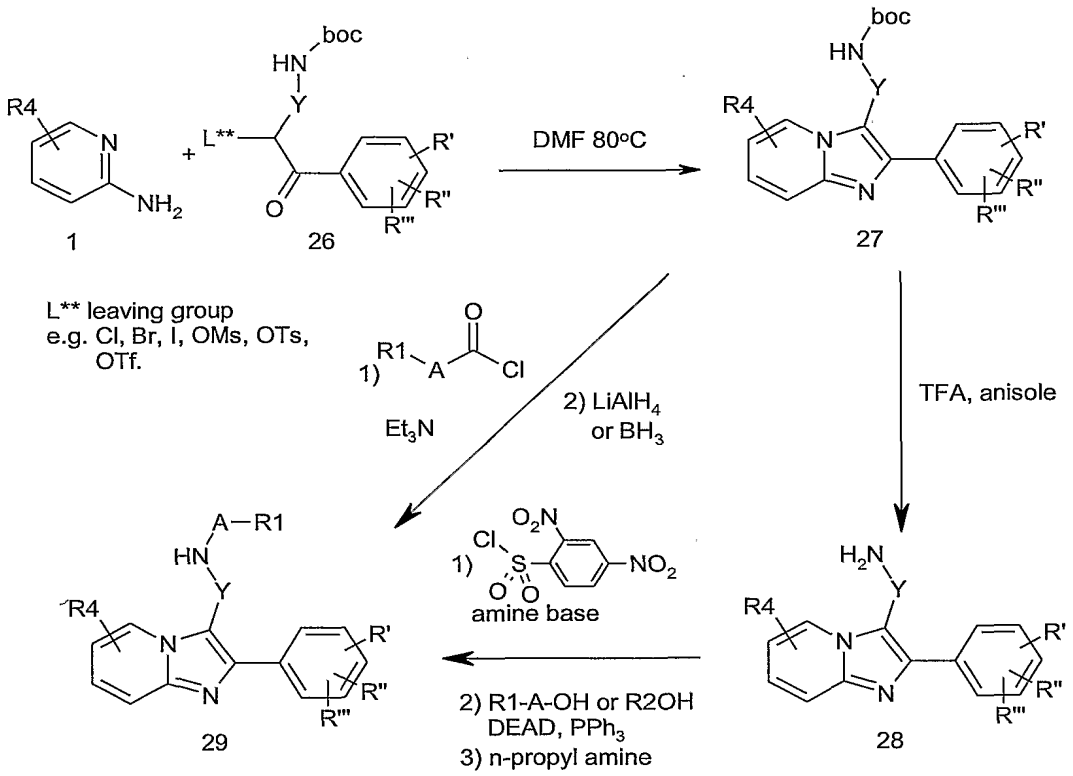


Scheme e.

Condensation of a suitable 2-aminopyridine **1** and a substituted aryl ketone **20**using the conditions described above gives imidazo[1,2-*a*]pyridines of the type **21** where a 3-position is already substituted with an alkyl chain. The leaving group L* can be converted

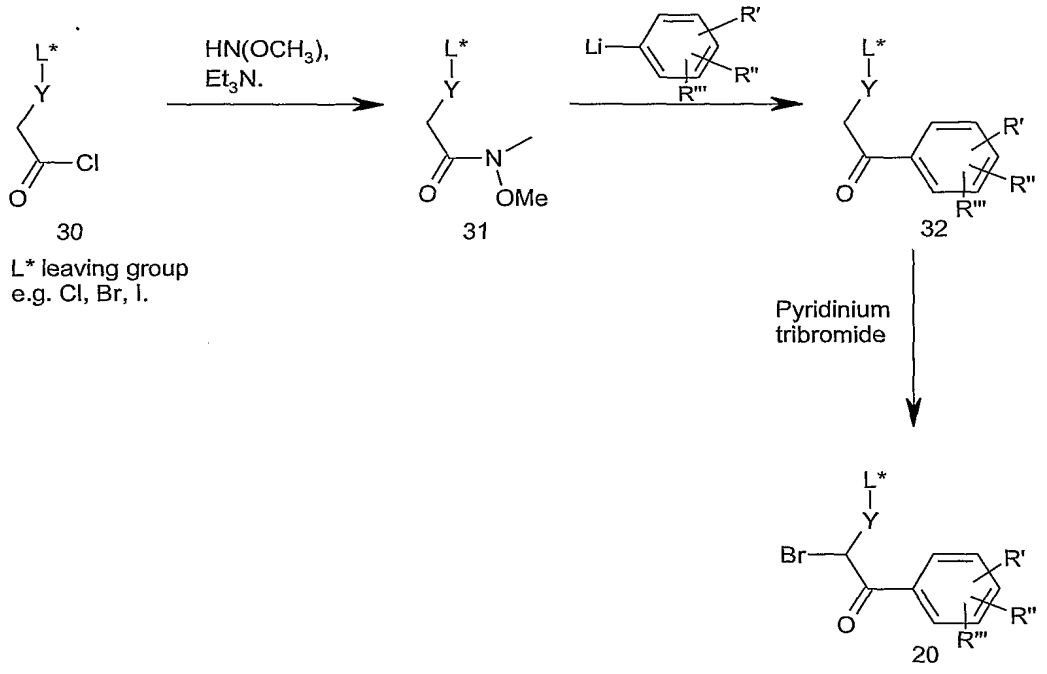
to an amine (**22**) by either the two step route of :- displacement with potassium phthalimide (heating in a suitable inert solvent such as DMSO, DMF or THF and mixtures thereof, and the like) then removal of the phthalimide protecting group (treatment with hydrazine in an inert solvent e.g. methylene chloride, chloroform, THF and mixtures thereof and the like), or displacement with sodium azide (heating in a suitable solvent DMSO, DMF or THF and mixtures thereof and the like) then reduction of the resultant azide (by treatment with hydrogen gas at atmospheric pressure or under high pressure [up to 600 psi] under palladium catalysis, or by Stoedinger reduction with triphenylphosphine). Groups R1 and R2 can be introduced by a modified Mitsunobu reaction. Reaction with an arylsufonyl chloride such as 2-nitrobenzenesulphonyl chloride, 4-nitrobenzenesulphonyl chloride, 2,4-nitrobenzenesulphonyl chloride and a hindered amine base such as 2,4,6-collidine, 2,6-lutidine or the like in an inert organic solvent such as methylene chloride, provides the corresponding sulfonamide. Mitsunobu coupling of the sulfonamide and an alcohol (R1OH or R2OH) can be achieved by treatment with an activating agent such as diethyldiazocarboxylate (DEAD), diisopropyldiazocarboxlate or the like with triphenylphosphine, tri-butylphosphine and the like, in an inert solvent such as benzene, toluene, tetrahydrofuran or mixtures thereof to give the dialkylated sulfonamide adduct. Removal of the sulfonamide group is accomplished by treatment with a nucleophilic amine such as *n*-propylamine to give substituted amine **23.**

The primary amine **22** can be converted to a cyano-guanidine (**24**) by the two step process of reaction with diphenyl cyanocarbonimidate in an inert organic solvent such as methylene chloride, chloroform, benzene, tetrahydrofuran and the like, followed by condensation with an appropriately substituted amine (HNR5R6) in an inert organic from the list above. Similarly, reaction with 1,1'-bis(methylthio)-2-nitroethylene in an inert solvent such methylene chloride, chloroform, benzene, tetrahydrofuran and the like, followed by condensation with an appropriately substituted amine (HNR5R6) in an inert organic solvent from the list above yields the nitroethyleneimidazo[1,2-*a*]pyridine **25.**



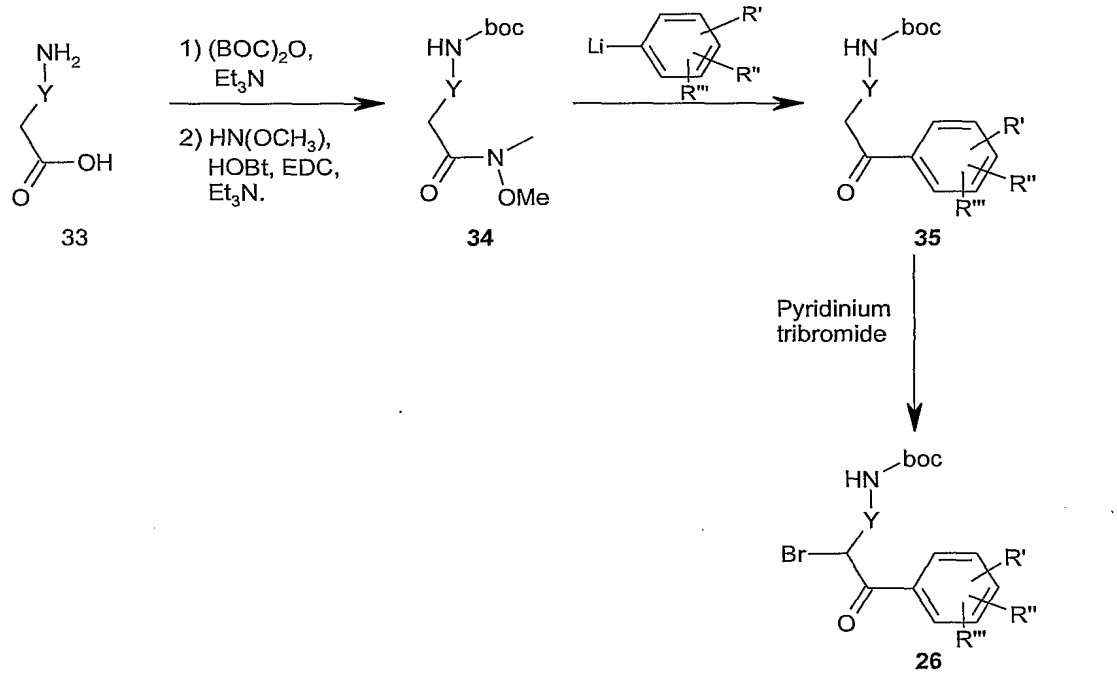
Scheme f

Condensation of 2-aminopyridines **1** with ketones bearing a *t*-butylcarbamate protected nitrogen atom (**26**) produces imidazo[1,2-*a*]pyridines such as **27**, where the nitrogen atom is already installed (Scheme f). The *t*-butylcarbamate protecting group is removed by treatment with an organic acid such as trifluoroacetic acid and the like, in the presence of a carbocation scavenger such as anisole, to yield the same imidazo[1,2-*a*]pyridines **28** as in scheme f. In the same manner the substitutents on the nitrogen atom can be installed by the Mitsunobu strategy (**28**→**29**) or by condensation with an acid chloride in the presence of a hindered amine base such as triethylamine, in an inert solvent such as methylene chloride, then reduction of this product with lithium aluminium hydride, in an inert solvent such as tetrahydrofuran, or by reduction with borane in a similarly inert solvent (**27**→**29**).



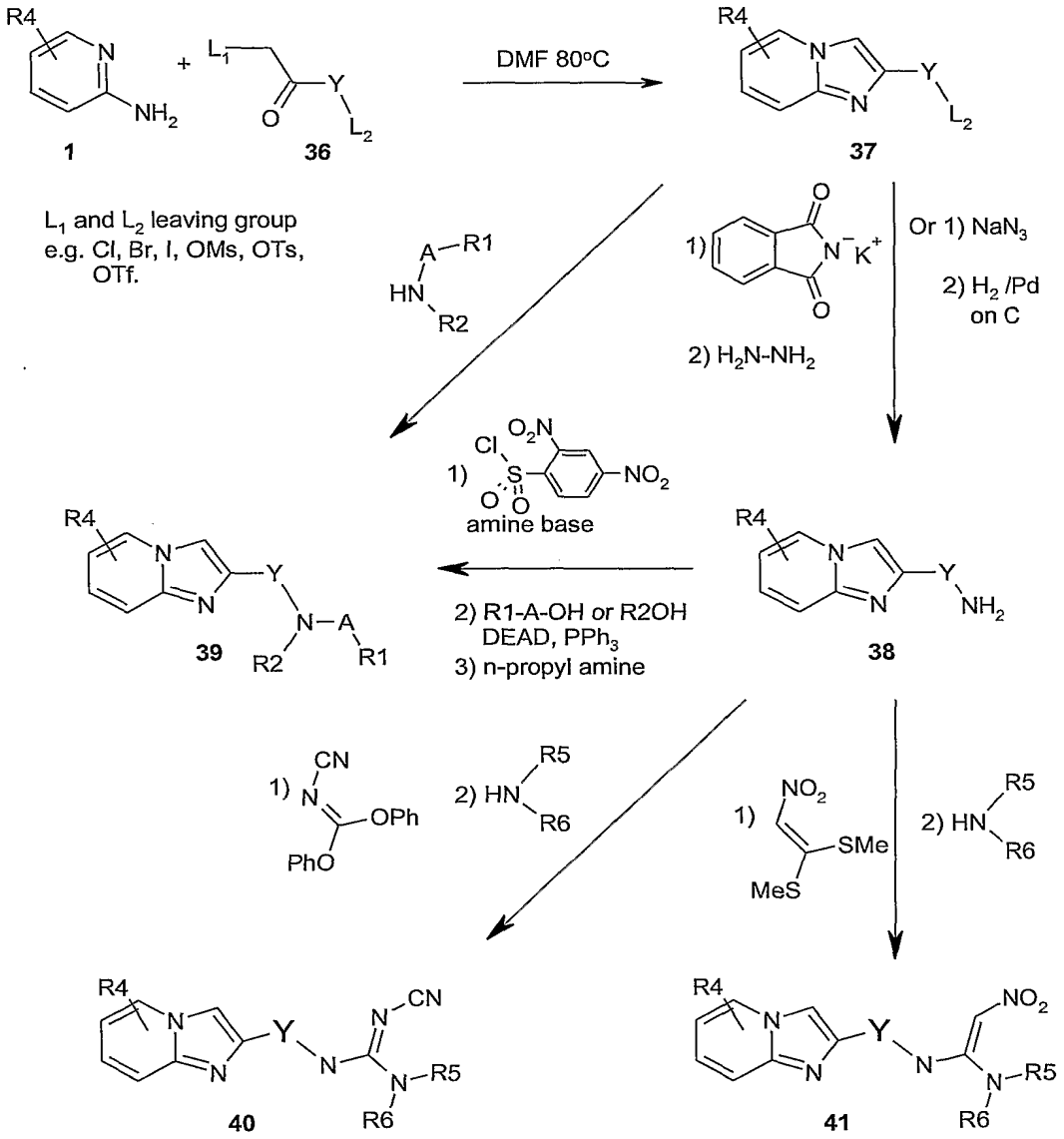
Scheme g.

Substituted ketones (**20**) can be prepared, as outlined in Scheme g starting from appropriate acid chlorides such as **30**. Treatment of the acid chloride with *N,N*-dimethylhydroxylamine in the presence of an amine base such as triethylamine, and a suitable solvent such as methylene chloride at a temperature of -10 °C to 25 °C, yields the amide **31**. Further reaction with a substituted aryl organolithium (prepared essentially as described in Wakefield B, J.; *Organolithium Methods* Academic Press Limited, **1988**, pp. 27-29 and references therein) in an inert solvent such as tetrahydrofuran, diethyl ether, benzene, toluene or mixture thereof and the like, at a temperature between -100 °C and O °C then quenching of the reaction mixture with a mineral acid such as hydrochloric acid, yields the aryl ketone **32**. Finally treatment of **32** with a bromine source such as pyridinium tribromide or pyrrolidone hydrobromide in an inert solvent such as chloroform or methylene chloride at -10 °C to 25 °C, yields a bromoketone **20** which is appropriate for the formation of an imidazo[1,2-*a*]pyridine.



Scheme h.

Commencing with a readily available amino acid with a suitable chain length for Y (**33**), the nitrogen atom can be installed directly by the route shown in Scheme h. Protection of the amine group of **33** with a *tert*-butylcarbamate group is achieved by condensation with di-*tert*-butyl dicarbonate in the presence of an amine base, for example triethylamine, in an inert solvent such as methylene chloride, chloroform, benzene, toluene, tetrahydrofuran and mixtures thereof and the like, at a temperature of -10 °C to 25 °C. Coupling of the acid product with *N,N*-dimethylhydroxylamine in the presence of a coupling reagent 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) or 1,3-dicyclohexylcarbodiimide (DCC) or the like, with or without 1-hydroxybenotriazole (HOBt), and suitable amine base, such as triethylamine and the like, in an inert solvent such as methylene chloride, chloroform, dimethylformamide, or mixture thereof, at or near room temperature for a period of 3 to 24 h provided the corresponding coupled product **34**. Following the same route described above for scheme g, the aryl group can then be installed and subsequently the α-bromo group to give the ketone **26**, which is suitable for condensation with a 2-aminopyridine.

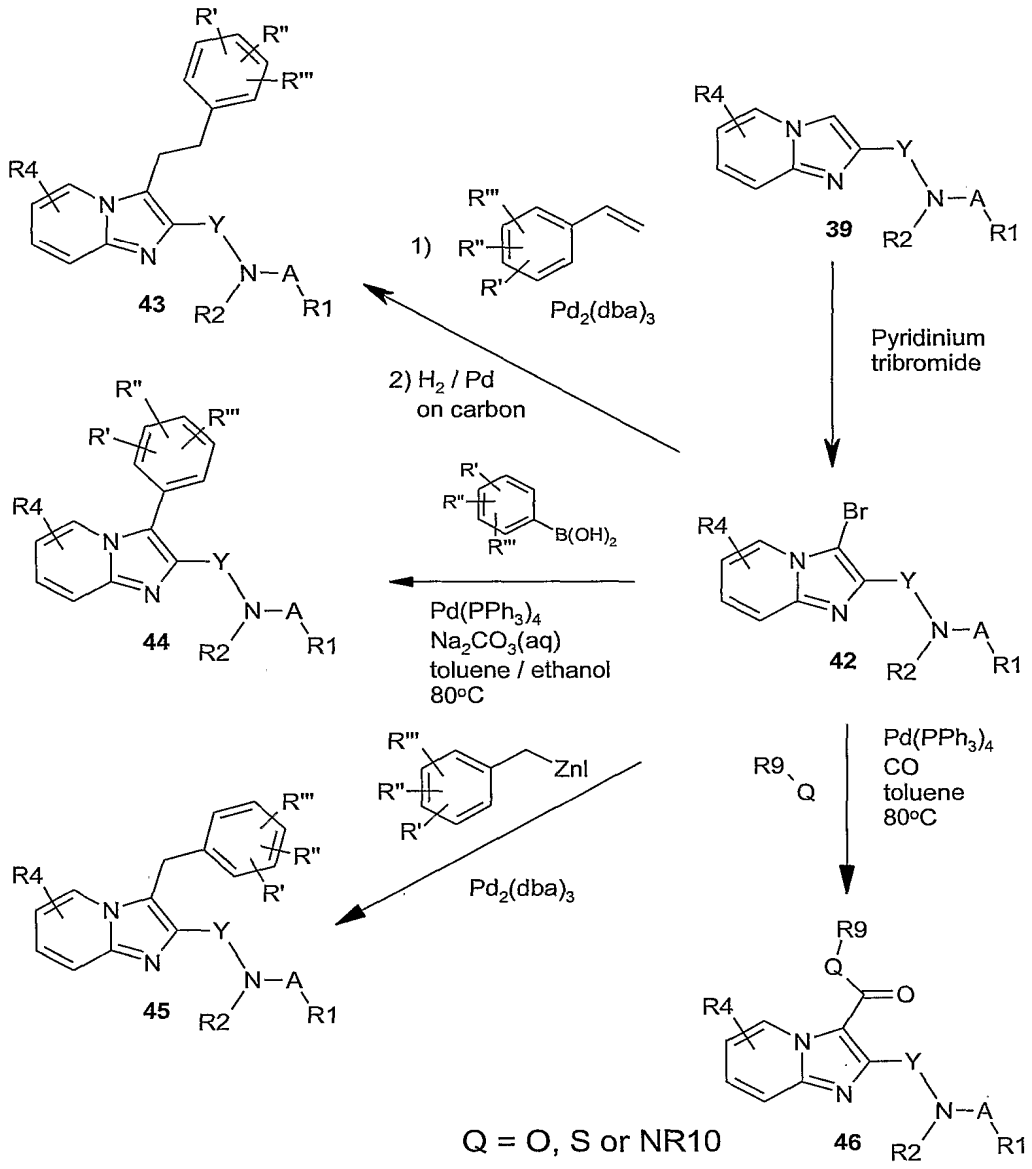


Scheme j

An isomeric series of imidazo[1,2-*a*]pyridines can be synthesised as described in Scheme j. Condensation of a suitably substituted 2-aminopyridine **1**, under the general conditions described above, with a ketone bearing two leaving groups α to the carbonyl (**36**) yields an imidazo[1,2-*a*]pyridine such as **37**. The substituted amino group can be installed by direct alkylation to yield **39**, or by an indirect multistep route as shown above

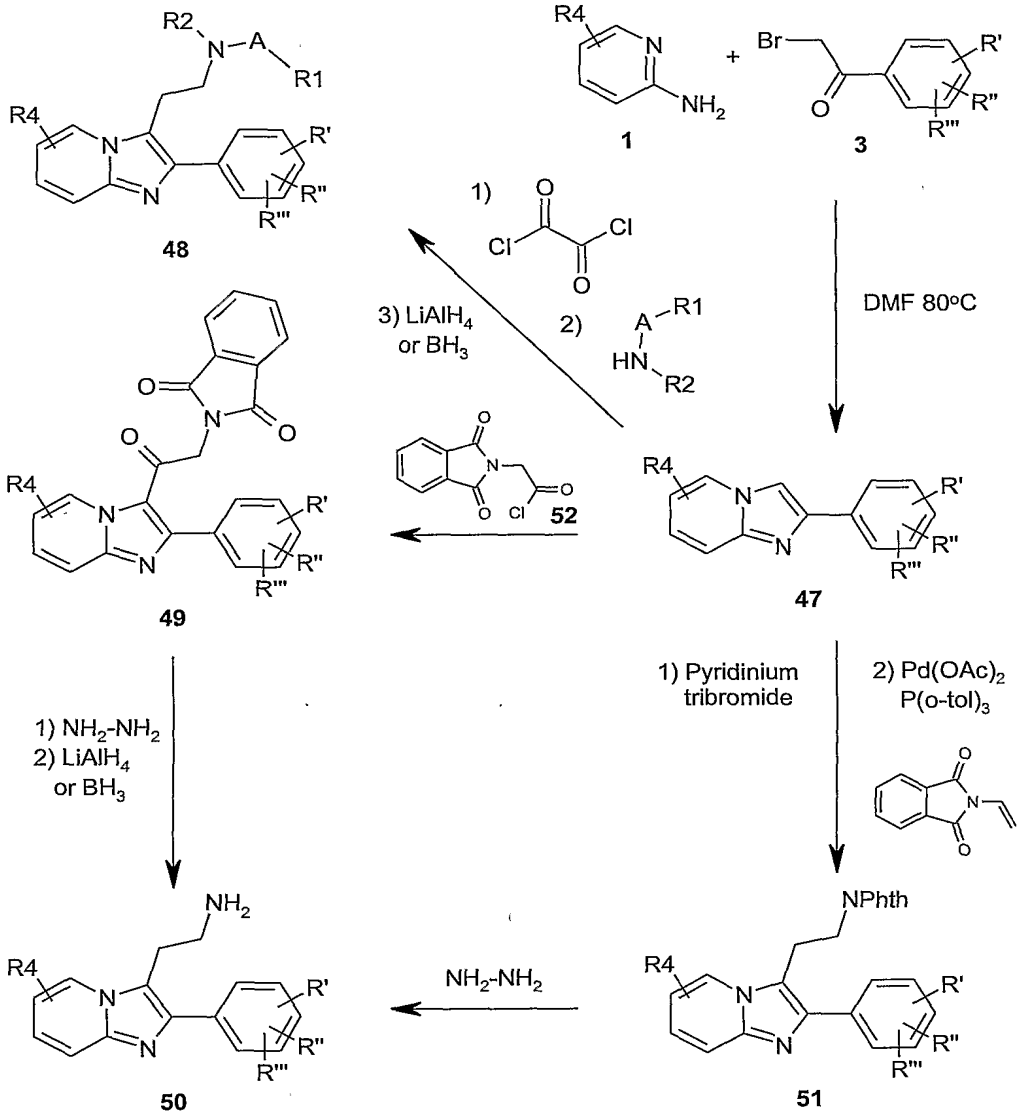
in scheme j (compound **37** to compound **38** via intermediate **39**), both routes are analogous to those shown in Schemes e.

In addition the amine group can be elaborated further to a cyano-guanidine **40** or a nitroethylene moiety such as compound **41** by the same methods as described in Scheme e.



Scheme k.

Treatment of the imidazo[1,2-*a*]pyridine **39** with molecular bromine, pyridinium tribromide, poly (vinyl pyridinium tribromide) or pyrrolidone hydrobromide in an inert solvent such as chloroform or methylene chloride at -10 °C to 25 °C installs a bromo group at the two position (**42**). The compound QR9 is suitable for palladium (0) catalysed reactions, for example treatment with carbon monoxide at 1 atm or higher pressure in the presence of a substituted amine (Q=NR10), alcohol (Q=O) or thiol (Q=S) in an inert solvent such as toluene, benzene, dioxane, THF and the like, yields 5-carbonyl-2-aryl-3-aminomethylimidazo[1,2-*a*]pyridines such as **46**. Again, treatment under palladium(0) catalysis with a weak base such aqueous sodium carbonate and the like and a substituted aryl boronic acid from commercial sources or prepared (as described in: Gronowitz, S.; Hornfeldt, A.-B.; Yang, Y.,-H *Chem. Sci.* **1986**, *26*, 311-314.) in an inert solvent such as toluene, benzene, dioxane, THF and the like, with heating between 25 °C and 100 °C, preferably 80 °C, for a period of 1-12 hours to give the imidazo[1,2-*a*]pyridine **44**. Similarly coupling of an arylalkylzinc iodide with **42** can be achieved using the method of Negishi (e.g. Jackson, R. F. W.; James, H.; Wythes, M. J.; Wood, A. *J. Chem. Soc. Chem. Commun.* **1989**, 644) yields imidazo[1,2-*a*]pyridines (**45**). Finally a Heck coupling reaction can be achieved using palladium (0) and a vinyl substituted aromatic compound in the presence of an organic amine base such as triethylamine and the like, in an inert solvent such as toluene, benzene, dioxane, THF and the like, with heating between 25 °C and 100 °C, preferably 80 °C, for a period of 1-12 hours to give the imidazo[1,2-*a*]pyridine **43**.



Scheme m.

Condensation of a suitable substituted 2-aminepyridine **1** with a bromoacetophenone **3** under the described conditions above, yields imidazo[1,2-*a*]pyridines such as **47**. A ethylamine group can be installed in several ways to yield compounds described by structure **50**. Reaction **47** with oxalylchloride in an inert solvent such as dichloromethane, 1,2-dichloroethane, benzene, toluene, tetrahydrofuran and mixtures thereof and the like, at a temperature between 0°C and 100°C, with or without the presence of an organic base, such as triethylamine, pyridine and the like, yields and acid chloride, which may be reacted *in-situ* by treatment with and appropriately substituted amine [HN(R2)-A-R1] in the

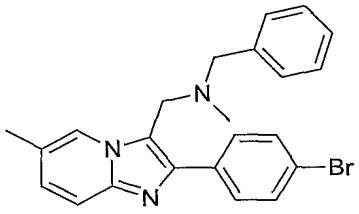
presence of an organic base such as triethylamine, pyridine and the like. The amide product from this step can then be reduced by an appropriate hydride reducing agent such as lithium aluminium hydride or borane in an appropriate inert solvent such as dichloromethane, 1,2-dichloroethane, benzene, toluene, tetrahydrofuran, thus, a fully substituted compound such as **48** can be synthesised.

Treatment of **47** with acid chloride **52** [prepared as described by Hubschwerlen, C,; Specklin, J.-L; *Org. Synth.* **1993**, *73*, 14] in an inert solvent such as dichloromethane, 1,2-dichloroethane, benzene, toluene, tetrahydrofuran and mixtures thereof and the like, at a temperature between 0°C and 100°C, with or without the presence of an organic base, such as triethylamine, pyridine and the like, yields the imidazo[1,2-*a*]pyridines **49**. Removal of the phthalimide protecting group by treatment with hydrazine, then reduction of the carbonyl group by an appropriate hydride reducing agent, such as lithium aluminium hydride or borane, in an appropriate inert solvent such as dichloromethane, 1,2-dichloroethane, benzene, toluene, tetrahydrofuran, yields the amine **50**, which may then be elaborated as shown in the earlier schemes.

Reaction of imidazo[1,2-*a*]pyridines **47** with a bromine source such as pyridinium tribromide or pyrrolidone hydrobromide in an inert solvent such as chloroform or methylene chloride at -10 °C to 25 °C, yields 3-bromo substituted imidazo[1,2-*a*]pyridines, which in turn can be treated with *N*-vinylphthalimide using Heck coupling conditions of palladium (0) catalysis in the presence of an organic amine base such as triethylamine and the like, in an inert solvent such as toluene, benzene, dioxane, THF and the like, with heating between 25 °C and 100 °C, preferably 80 °C, for a period of 1-12 hours to give the imidazo[1,2-*a*]pyridine **51**. Finally treatment with hydrazine under standard conditions yields the 3-ethylamine imidazo[1,2-*a*]pyridine **50**, which again may be elaborated as shown in the earlier schemes.

EXAMPLES

Example A1 - Preparation of *N*-Benzyl-*N*-methyl-2-(4-bromophenyl)-3-methylamino-5-methylimidazo[1,2-*a*]pyridine.



Step A1: 2-(4-bromophenyl)-5-methyl-imidazo[1,2-*a*]pyridine.

A mixture of 2-amino-5-picoline (2.00 g 18.5 mmol) and 2,4'-dibromoacetophenone (5.10 g 18.5 mmol) in DMF (20 mL) was heated at 80 °C for 1h 45 min. The mixture was cooled to RT then diluted with water (200 mL) and basified with 2M NaOH (aq) (150 mL). The mixture was extracted into EtOAc (2 × 200mL) and the extracts dried ($MgSO_4$) and concentrated *in vacuo* to give the crude title compound as a yellow solid (5.12 g 96%).

Mass Spectrum: m/e $C_{14}H_{12}BrN_2$ (M+H) 287.37 and 289.38 found.

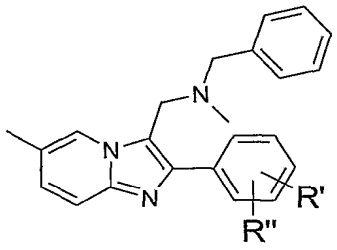
^{1}H NMR spectrum (DMSO-d_6): δ ^{1}H NMR (300 MHz, D6 -DMSO) 2.27 (3H, s); 7.11 (1H, d); 7.48 (1H, d); 7.61 (2H, d); 7.90 (2H, d); 7.94 (1H, s); 8.32 (1H, s).

Step A2:*N*-Benzyl-*N*-methyl-2-(4-bromophenyl)-3-methylamino-5-methylimidazo[1,2-*a*]pyridine.

A mixture of 2-(4-bromophenyl)-5-methyl-imidazo[1,2-*a*]pyridine(4.96 g 17.3 mmol), paraformaldehyde (518 mg 17.3 mmol) and benzylmethylamine(2.23 mL 17.3mmol) in acetic acid (9 mL) was heated for 2h at 60 °C. The majority of the solvent was removed *in vacuo* and the mixture rediluted with EtOAc (400 mL) and washed with 2M NaOH (aq) (2 × 150mL). The solution was dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatograpy (silica gel, slow gradient neat CH_2Cl_2 to 6% MeOH) gave the title

compound as an orange oil (3.86 g 53%). HCl salt of title compound was prepared by the addition of 1.0M HCl in diethyl ether (23 mL) to a solution of the title compound in EtOAc (4 mL). The salt was precipitated with diethyl ether and collected by centrifuge.

Following a procedure similar to that described in Example 1, the following compounds were prepared.

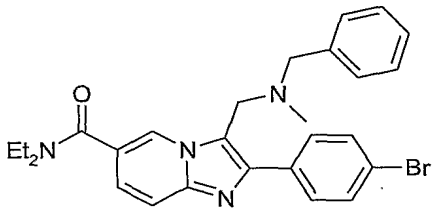


Example No.	R'	R"	δ 1H NMR (300 MHz D6-DMSO)	m/e (ESP+) (MH+)
A1 **N-Benzyl-N-methyl-2-(4-bromophenyl)-3-methylamino-5-methylimidazo[1,2-a]pyridine.**	4-Br	H	2.04 (3H, s); 2.31 (3H, s); 3.52 (2H, s); 3.96 (2H, s); 7.15 (1H, d); 7.20 - 7.30 (5H, m); 7.49 (1H, d); 7.63 (2H, d); 7.84 (2H, d); 8.31 (1H, s).	420 422
A2 **N-Benzyl-N-methyl-2-(4-chlorophenyl)-3-methylamino-5-methylimidazo[1,2-a]pyridine**	4-Cl	H		362 364
A3	4-F	H	2.40 (3H, s), 2.47 (3H, s),	360

***N*-Benzyl-*N*-methyl-2-(4-fluorophenyl)-3-methylamino-5-methylimidazo[1,2-*a*]pyridine**			4.20 (1H, s), 4.55 (1H, s), 5.00 (2H, s), 7.38-7.57 (6H, m), 7.86-7.97 (m, 4H), 9.15 (0.5H, s) and 11.64 (0.5H, s).	
A4 ***N*-Benzyl-*N*-methyl-2-(4-cyanophenyl)-3-methylamino-5-methylimidazo[1,2-*a*]pyridine**	4-CN	H	2.41 (3H, s), 2.44 (3H, s), 4.23 (1H, s), 4.53 (1H, s), 5.02 (2H, s), 7.43 (3H, s), 7.54 (2H, s), 7.73 (1H, d), 7.85 (1H, d), 8.02 (4H, s), 8.92 (0.5H, s) and 11.17 (0.5H, s).	367
A5 ***N*-Benzyl-*N*-methyl-2-(4-methoxyphenyl)-3-methylamino-5-methylimidazo[1,2-*a*]pyridine**	4-OMe	H	2.40 (3H, s), 2.47 (3H, s), 3.86 (3H, s), 4.20 (1H, s), 4.54 (1H, s), 5.00 (2H, s), 7.16 (2H, d), 7.42 (3H, s), 7.55 (2H, s), 7.75 (2H, d), 7.91 (2H, s), 9.05 (0.5H, s) and 11.47 (0.5H, s).	372
A6 ***N*-Benzyl-*N*-methyl-2-(3,4-dimethoxyphenyl)-3-methylamino-5-methylimidazo[1,2-*a*]pyridine**	4-OMe	3-OMe	2.39 (3H, s), 2.48 (3H, s), 3.84 (3H, s), 3.85 (3H, s), 4.24 (1H, s), 4.57 (1H, s), 5.03 (2H, s), 7.14 (1H, d), 7.37 (2H, d), 7.41 (3H, s), 7.92 (2H, s), 9.08 (0.5H, s) and 11.50 (0.5H, s).	402
A7 ***N*-Benzyl-*N*-methyl-2-(3,4-dichlorophenyl)-3-**	4-Cl	3-Cl	2.37 (3H, s), 2.46 (3H, s), 4.12 (1H, s), 4.54 (1H, s), 4.70 (2H, s), 4.87 (1H, s),	410 412

methylamino-5-methylimidazo[1,2-*a*]pyridine			7.42 (3H, s), 7.53 (2H, S), 7.67 (1H, d), 7.70 (1H, d), 7.85 (1H, d), 7.94 (2H, s), 9.06 (0.5H, s) and 11.44 (0.5H, s).	

Example B1 - Preparation of *N*-Benzyl-*N*-methyl-2-(4-bromophenyl)-5-diethylamido-3-methylamino-imidazo[1,2-*a*]pyridine.



Step B1: **2-(4-bromophenyl)-5-carboxy-imidazo[1,2-*a*]pyridine.**

A mixture of 6-aminonicotinic acid (1.00 g 7.24 mmol) and 2,4'-dibromoacetophenone (4.02 g 14.5 mmol) in DMF (10 mL) was heated at 60 °C for 24 h. The mixture was cooled to RT then partitioned between water (200 mL) and EtOAc (250mL). The yellow precipitate between the two layers was removed by filtration and dried by high vacuum to yield the title compound (1.72 g 75%).

Mass Spectrum: m/e $C_{14}H_{10}BrN_2O_2$ (M+H) 317.16 and 319.16 found.

Step B2: **2-(4-bromophenyl)-5-diethylamido-imidazo[1,2-*a*]pyridine.**

HOBt (426 mg 3.15mmol) was added in one portion to a stirred solution of 2-(4-bromophenyl)-5-carboxylic-imidazo[1,2-*a*]pyridine (1.00 g 3.15 mmol) and EDC (605 mg 3.15 mmol) in CH_2Cl_2 (30 mL) under N_2 at O°C. The mixture was stirred for 1h then

diethylamine (1.63 mL 15.8 mmol) was added and the mixture allowed to stir at RT for 20h. After this time the solvent was removed *in vacuo* then the mixture rediluted with EtOAc (250 mL) then washed with 1M citric acid (200 mL) then saturated $NaHCO_3$ (aq) (200 mL) and brine (200 mL). The organic solution was dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound as a yellow solid (601 mg 51%).

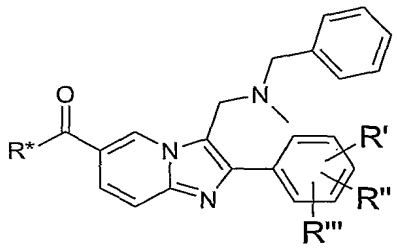
Mass Spectrum: m/e $C_{18}H_{18}BrN_2O_2$ (M+H) 272.20 and 274.23 found.

^{1}H NMR spectrum (DMSO-d_6): δ ^{1}H NMR (300 MHz, D6 -DMSO) 1.15 (6H, t), 3.18 (4H, m); 7.12 (1H, d); 7.30 (1H, d); 7.33 (2H, d); 7.93 (2H, d); 8.44 (1H, s); 8.68 (1H, s).

Step B3: ***N*-Benzyl-*N*-methyl-2-(4-bromophenyl)-5-diethylamido-3-methylamino-imidazo[1,2-*a*]pyridine.**

A mixture of 2-(4-bromophenyl)-5-diethylamido-imidazo[1,2-*a*]pyridine (300 mg 0.806 mmol), paraformaldehyde (26.0 mg 0.812 mmol) and benzylmethylamine(100 μL 0.806 mmol) in acetic acid (2 mL) was heated for 1h at 50 °C. The majority of the solvent was removed *in vacuo* and the mixture rediluted with EtOAc (200 mL) and washed with 2M NaOH (aq) (2 × 150mL). The solution was dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatograpy (silica gel, slow gradient neat CH_2Cl_2 to 6% MeOH) gave the title compound as an yellow oil (276 mg 68%). HCl salt of title compound was prepared by the addition of 1.0M HCl in diethyl ether (150 μL) to a solution of the title compound in EtOAc (500 μL). The salt was precipitated with diethyl ether and collected by centrifuge.

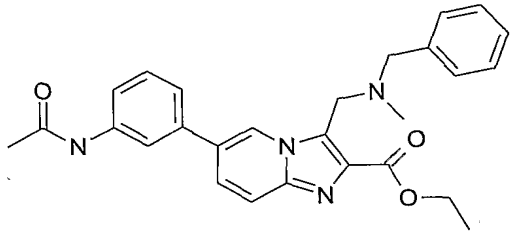
Following a procedure similar to that described in Example 1, the following compounds were prepared.



Example No.	R'	R"	R'"	R*	δ 1H NMR (300 MHz, D6 - DMSO)	m/e (M+H)
B1 <u>*N*-Benzyl-*N*-methyl-2-(4-bromophenyl)-5-diethylamido-3-methylamino-imidazo[1,2-*a*]pyridine</u>	4-Br	H	H	Et_2N	1.05 - 1.13 (6H, b); 2.04 (3H, s); 3.39 (4H, b); 3.50 (2H, s); 4.09 (2H, s); 7.16 - 7.29 (5H, m); 7.32 (1H, d); 7.62 (1H, d); 7.70 (2H, d); 7.86 (2H, d); 8.58 (1H, s).	505 507
B2 <u>*N*-Benzyl-*N*-methyl-2-(4-bromophenyl)-5-isopropyloxycarbonyl-3-methylamino-imidazo[1,2-*a*]pyridine</u>	4-Br	H	H	*i*PrO	1.20 (6H, d); 1.98 (3H, s); 3.59 (2H, b); 4.15 (2H, s); 7.21 - 7.33 (5H, m); 7.62 - 7.74 (4H, m); 7.75 - 7.83(4H, m); 9.25 (1H, s).	492 494
B3 <u>*N*-Benzyl-*N*-methyl-2-(4-isopropylamidophenyl)-5-isopropyloxycarbonyl-3-methylamino-imidazo[1,2-</u>	4-NHC(O)*i*Pr	H	H	*i*PrO	1.12 (6H, d); 1.38 (6H, d); 1.97 (3H, s); 2.64 (1H, 'q'); 3.57 (2H, s); 4.16 (2H, s); 5.21 (1H, 'q'); 7.20 -	499

a]pyridine					7.32 (5H, m); 7.63 (1H, d); 7.70 (1H, d); 7.75(4H, 's'); 9.28 (1H, s); 9.92 (1H, s).	
B4 **N-Benzyl-N-methyl-2-(3,4,5-trimethylphenyl)-5-diethylamido-3-methylamino-imidazo[1,2-a]pyridine**	3-Me,	Me	4-Me	Et_2N	1.16 (6H, b); 2.20 (3H, s); 2.26 (3H, s); 2.37 (6H, s); 3.48 (4H, b); 3.54 (2H, s); 4.04 (2H, s); 7.18 - 7.32 (6H, m); 7.46 (2H, s); 7.63 (1H, d); 8.58 (1H, s).	469

Example C - Preparation of Ethyl *N*-benzyl-*N*-methyl-5-(3-acetamidophenyl)-3-methylamino-imidazo[1,2-*a*]pyridine-2-carboxylate.



Step C1: **Ethyl 5-bromo-imidazo[1,2-*a*]pyridine-2-carboxylate.**

A mixture of 2-amino-5-bromopyridine (1.00 g 5.78 mmol) and ethyl bromopyruvate (0.730 mL 5.78 mmol) in DMF (10 mL) was heated at 80 °C for 2 h. The mixture was cooled to RT then partitioned between water (200 mL) and EtOAc (250mL). The aqueous layer was extracted again with EtOAc (2 × 100mL) and the combined extracts dried

($MgSO_4$) and concentrated *in vacuo* to yield the crude title compound as a yellow solid (1.24 g 80%).

Mass Spectrum: m/e $C_{10}H_9BrN_2O_2$ (EP+) (MH+) 264 and 271 found.

^{1}H NMR spectrum (DMSO-d_6): δ ^{1}H NMR (300 MHz, D6 -DMSO) 1.31 (3H, t), 4.31 (2H, q); 7.46 (1H, d); 7.61 (1H, d); 7.33 (2H, d); 8.45 (1H, s); 8.89 (1H, s).

Step C2: **Ethyl *N*-Benzyl-*N*-methyl-5-bromo-3-methylamino-imidazo[1,2-*a*]pyridine-2-carboxylate.**

A mixture of ethyl 5-bromo-imidazo[1,2-*a*]pyridine-2-carboxylate (1.24 g 4.61 mmol), paraformaldehyde (138 mg 4.61 mmol) and benzylmethylamine(600 μL 4.61 mmol) in acetic acid (15 mL) was heated for 1h at 50 °C. The majority of the solvent was removed *in vacuo* and the mixture rediluted with EtOAc (250 mL) and washed with 2M NaOH (aq) (3 × 150mL). The solution was dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatograpy (silica gel, slow gradient neat CH_2Cl_2 to 10% MeOH) gave the title compound as an yellow oil (980 mg 53%).

Mass Spectrum: m/e $C_{19}H_{20}BrN_3O_2$ (EP+) (MH+) 264 and 271 found.

^{1}H NMR spectrum (DMSO-d_6): δ ^{1}H NMR (300 MHz, D6 -DMSO) 1.32 (3H, t); 2.08 (3H, s); 3.58 (2H, s); 4.22 (2H, s); 4.33 (2H, q); 7.21 - 7.34 (5H, m); 7.50 (1H, d); 7.59 (1H, d); 8.57 (1H, s).

Step C3: **Ethyl *N*-benzyl-*N*-methyl-5-(3-acetamidophenyl)-3-methylamino-imidazo[1,2-*a*]pyridine-2-carboxylate.**

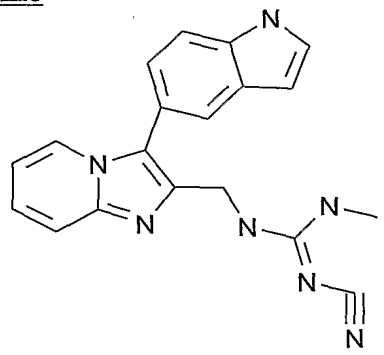
Tetrakis(triphenylphosphine) palladium(0) (58.0 mg 0.050 mmol) was added in one portion to a degassed mixture of ethyl *N*-Benzyl-*N*-methyl-5-bromo-3-methylamino-imidazo[1,2-*a*]pyridine-2-carboxylate (200 mg 0.498 mmol) and N-acetyl-3-aminobenzeneboronic acid (89.0 mg 0.498 mmol) in toluene (2 mL), ethanol (2 mL) and saturated $NaHCO_3$ (aq) (1 mL). The mixture was heated at 80 °C with vigorous stirring for

4 h then cooled to RT. The mixture was diluted with EtOAc (200 mL) and washed with water (100 mL) and brine (100 mL) then dried ($MgSO_4$). The solution was concentrated in vacuo and the product isolated by flash column chromatography (3 runs on silica slow gradient neat CH_2Cl_2 to 20% MeOH). This gave the title compound as a colourless oil (27.0 mg 12%).

Mass Spectrum: m/e $C_{27}H_{28}N_4O_3$ (EP+) (MH+) 456 found.

^{1}H NMR spectrum (DMSO-d_6): δ ^{1}H NMR (300 MHz, $CDCl_3$) 1.46 (3H, t); 2.21 (3H, s); 2.25 (3H, s); 3.61 (2H, s); 4.23 (2H, s); 4.48 (2H, q); 7.15 - 7.29 (5H, m); 7.29 - 7.37 (1H, m); 7.38 - 7.49 (3H, m); 7.76 (1H, s); 7.89 (1H, s); 8.39 (1H, s). HCl salt of title compound was prepared by the addition of 1.0M HCl in diethyl ether (177 µL) to a solution of the title compound in EtOAc (300 µL). The salt was precipitated with diethyl ether and collected by centrifuge.

Example D1 - Preparation of *N*-Cyano-*N'*-[3-(1H-indol-5-yl)-imidazo[1,2-*a*]pyridin-2-ylmethyl]-*N''*-methyl-guanidine



Step D1: Preparation of 1-Imidazo[1,2-a]pyridin-2-ylmethyl-3-cyano-2-phenyl-isourea

A mixture of 2-aminomethylimidazo[1,2-*a*]pyridine (1.20 g, 9.00 mmol) and diphenyl-cyanocarbonimidate (2.35 g, 9.90 mmol) in IPA were stirred at ambient temperature for 4 h. The cloudy reaction gave rise to a precipitate which was filtered. This was washed with

ether and dried to yield the title compound as a white solid (1.55 g, 59 %). **Mass Spectrum:** 292 [MH]+

Step D2: Preparation of *N*-Cyano-*N'*-(imidazo[1,2-*a*]pyridin-2-ylmethyl)-*N''*-methyl-guanidine

A mixture of 1-imidazo[1,2-*a*]pyridin-2-ylmethyl-3-cyano-2-phenyl-isourea (1.00 g, 3.40 mmol) and excess methylamine in 33% aq. ethanol (5 mL) in IPA were warmed to 70 °C for 2 h. The reaction was concentrated *in vacuo*, and the residue triturated with ethyl acetate and filtered. The resulting solid was washed with ether and dried to give the title compound as a white solid (0.75 g, 97%).

Mass Spectrum: 229 [MH]+

^{1}H NMR spectrum (DMSO-d_6): 2.72 (3H, s); 4.40 (2H, s); 6.82 (1H, t); 7.17 (1H, brs), 7.19 (1H, t); 7.40 (1H, br s); 7.48 (1H, d); 7.78 (1H, s); 8.48 (1H, d).

Step D3: *N*-Cyano-*N'*-(3-bromo-imidazo[1,2-*a*]pyridin-2-ylmethyl)-*N''*-methyl-guanidine

A mixture of *N*-Cyano-*N'*-(imidazo[1,2-*a*]pyridin-2-ylmethyl)-*N''*-methyl-guanidine (0.300 g, 1.30 mmol), poly(4-vinylpyridinium tribromide) (0.467 g, 1.40 mmol), pyridine (2 drops) in CH_2Cl_2 were stirred at ambient temperature for 16 h. DMF was added, the solid support filtered off, and the mother liquors concentrated *in vacuo*. The residue was triturated with CH_2Cl_2 and the resulting solid filtered to yield the title compound as a fawn solid (0.390 g, 98%).

Mass Spectrum: 307, 309 [MH]+

^{1}H NMR spectrum (DMSO-d_6): 2.76 (3H, d); 4.46 (2H, d); 7.21 (1H, d); 7.24 (1H, t); 7.45 (1H, t); 7.58 (1H, t); 7.76 (1H, d); 8.45 (1H, d)

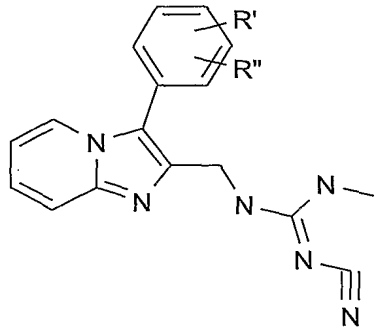
Step D4: Preparation of *N*-Cyano-*N'*-[3-(1H-indol-5-yl)-imidazo[1,2-*a*]pyridin-2-ylmethyl]-*N''*-methyl-guanidine

To a mixture of *N*-Cyano-*N'*-(3-bromo-imidazo[1,2-*a*]pyridin-2-ylmethyl)-*N''*-methyl-guanidine (700 mg, 0.230 mmol), 5-indolyl boronic acid (560 mg, 0.345 mmol), saturated Na_2CO_3 (1.5 mL), ethanol (0.60 mL) and toluene (3 mL) was added a catalytic amount of $Pd(PPh_3)_4$. The reaction was stirred at 80 °C for 16 h. The reaction was poured onto a hydromatrix column and eluted with CH_2Cl_2. Flash column chromatography (silica gel, slow gradient, neat CH_2Cl_2 to 5% MeOH:CH_2Cl_2) gave the title compound as a white solid (17.0 mg, 22%).

Mass Spectrum: 344 [MH]+

^{1}H NMR spectrum (DMSO-d_6): 2.89 (3H, d); 4.02 (2H, d); 5.85 (1H, t); 6.63 (1H, s); 6.88 (1H, t); 7.17- 7.27 (3H, m); 7.36 (1H , m); 7.57 (1H, d); 7.59 (1H, d); 7.66 (1H, s), 8.08 (1H, d); 8.78 (1H, br s)

Following a procedure similar to that described for Example D1, the following compounds were prepared.



Example No.	R'	R''	^{1}H NMR spectrum (DMSO-d_6):	Mass Spectrum [MH]+
D2	3-OMe	4-OMe	2.71(3H, d); 3.80 (3H, s); 3.86 (3H,	365

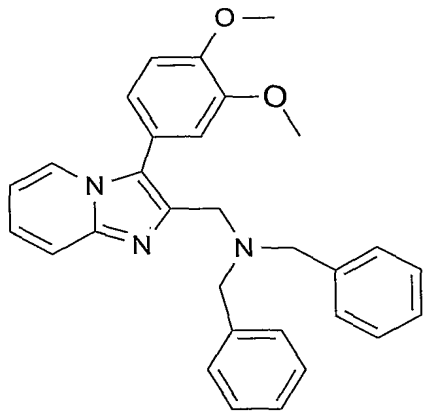
			s); 4.55 (2H, d); 7.21 (2H, s); 7.28 (2H, s) ; 7.43 (1H, t); 7.65 (1H, t); 7.90-8.03 (2H, m); 8.50 (1H, d)	
D3	4-Cl		2.69 (3H, d); 4.54 (2H, d); 7.30 (1H, d); 7.45 (1H, t); 7.73 (4H, s); 7.92-8.08 (3H, m); 8.52 (1H, d)	339
D4	3-Me	5-Me	2.41 (6H, s); 2.92 (3H, d); 4.42 (2H, d); 5.78 (1H, t); 6.81 (1H, t); 7.03 (2H, s); 7.15 (1H, s); 7.22 (2H, t); 7.57 (1H, d); 8.04 (1H, d)	333

D2 = *N*-Cyano-*N'*-[3-(3,4-dimethoxyphenyl)-imidazo[1,2-*a*]pyridin-2-ylmethyl]-*N''*-methyl-guanidine

D3 = *N*-Cyano-*N'*-[3-(4-chlorophenyl)-imidazo[1,2-*a*]pyridin-2-ylmethyl]-*N''*-methyl-guanidine

D4 = *N*-Cyano-*N'*-[3-(3,5-dimethylphenyl)-imidazo[1,2-*a*]pyridin-2-ylmethyl]-*N''*-methyl-guanidine

Example E - *N,N*-Dibenzyl-2-methylamino-3-(3,4-dimethoxyphenyl)imidazo[1,2-*a*]pyridine



Step E1: Preparation of *N,N*-Dibenzyl-2-methylaminoimidazo[1,2-*a*]pyridine

A mixture of 2-aminoethylimidazo[1,2-*a*]pyridine dihydrochloride (0.500 g, 2.26 mmol), benzyl bromide (0.430 g, 2.50 mmol) and powdered K_2CO_3 (1.56 g, 11.3 mmol) in DMF (20 mL) was heated at 100 °C for 2 h. The DMF was removed *in vacuo* and then residue taken into CH_2Cl_2 and filtered to remove inorganics. This was purified by flash column chromatography (silica gel, CH_2Cl_2 to 5% MeOH:CH_2Cl_2) to give the title compound as orange oil (0.405 g, 55%).

Mass Spectrum: 328 [MH]+

^{1}H NMR spectrum ($CDCl_3$): 3.68 (4H, s); 3.82 (2H, s); 6.74 (1H, t); 7.10 (1H, t); 7.18-7.48 (10H, m); 7.55 (1H, d); 7.60 (1H, s); 8.07 (1H, d)

Step E2: Preparation of *N,N*-Dibenzyl-2-methylamino-3-bromoimidazo[1,2-*a*]pyridine

A mixture of *N,N*-Dibenzyl-2-methylaminoimidazo[1,2-*a*]pyridine (0.380 g, 1.16 mmol), poly(4-vinylpyridinium tribromide) (0.387 g, 1.16 mmol), pyridine (2 drops) in CH_2Cl_2 (20 mL) were stirred at ambient temperature for 16 h. The solid support was filtered off

and the mother liquors concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, slow gradient, CH_2Cl_2 to 3:7 EtOAc:Hexane to 6:4 EtOAc:Hexane) to yield the title compound as a yellow oil (0.260 g, 55%).

Mass Spectrum: 406, 408 [MH]+

^{1}H NMR spectrum ($CDCl_3$): 3.70 (4H, s); 3.82 (2H, s); 6.90 (1H, t); 7.17-7.48 (11H, m); 7.58 (1H, d), 8.08 (1H, d)

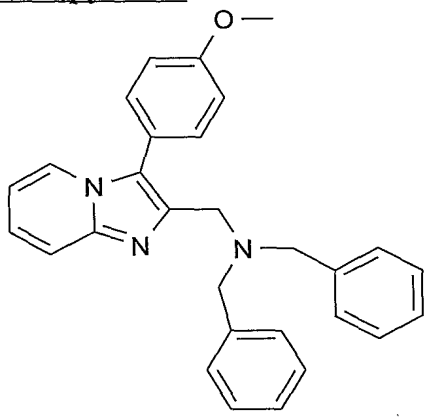
Step E3: Preparation of *N,N*-Dibenzyl-2-methylamino-3-(3,4-dimethoxyphenyl)imidazo[1,2-*a*]pyridine

To a mixture of *N,N*-Dibenzyl-2-methylamino-3-bromoimidazo[1,2-*a*]pyridine (150 mg, 0.370 mmol), 3,4-dimethoxybenzene boronic acid (81.0 mg, 0.440 mol), saturated Na_2CO_3 (2.5 mL), ethanol (0.90 mL) and toluene (4.50 mL), was added a catalytic amount of $Pd(PPh_3)_4$. The reaction was stirred at 80 °C for 3 h. The toluene layer was separated and concentrated *in vacuo*. Flash column chromatography (silica gel, slow gradient, neat CH_2Cl_2 to 3:7EtOAc:Hexane to 7:3 EtOAc:Hexane) gave the title compound as an oil. The HCl salt was prepared by addition of 1M HCl in diethyl ether to a solution of the compound in EtOAc to give the title compound dihydrochloride as a white solid (98.0 mg, 49%).

Mass Spectrum: 464 [MH]+

^{1}H NMR spectrum (DMSO-d_6): 3.75 (3H, s); 3.88 (3H, s); 4.08 (4H, br s); 4.15 (2H, brs); 7.05-7.19 (3H, m); 7.30 (7H, s); 7.46 (4H, s); 7.84 (1H, t); 8.00 (1H, d); 8.43 (1H, d)

Example F - Preparation of *N,N*-Dibenzyl-2-methylamino-3-(4-dimethoxyphenyl)imidazo[1,2-*a*]pyridine

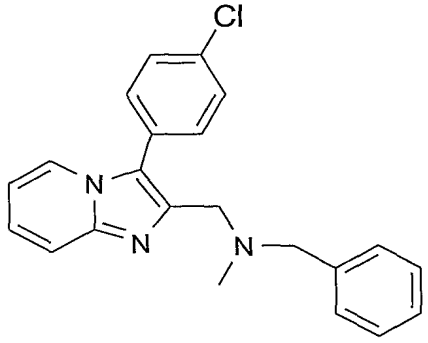


To a mixture of *N,N*-Dibenzyl-2-methylamino-3-bromoimidazo[1,2-*a*]pyridine (100mg, 0.25mmol), 4-methoxybenzene boronic acid (76.0 mg, 0.500 mol), saturated Na_2CO_3 (1.5 mL), ethanol (0.6 mL) and toluene (3 mL), was added a catalytic amount of $Pd(PPh_3)_4$. The reaction was stirred at 80 °C for 3 h.

The toluene layer was separated and concentrated *in vacuo*. Flash column chromatography (silica gel, slow gradient, neat CH_2Cl_2 to 3:7 EtOAc:Hexane to 7:3 EtOAc:Hexane) gave the title compound as an oil. The HCl salt was prepared by addition of 1M HCl in diethyl ether to a solution of the compound in EtOAc to give the title compound dihydrochloride as a white solid (41.0 mg, 32%)

Mass Spectrum: 434 [MH]+

Example G - Preparation of *N*-benzyl-*N*-methyl-2-methylamino-3-(4-chlorophenyl)imidazo[1,2-*a*]pyridine



Step G1: Preparation of 2-chloromethylimidazo[1,2-*a*]pyridine

A mixture of dichloroacetone (17.8 g, 14.0 mmol) and 2-aminopyridine (10.0 g , 11.0 mmol) in DMF (80 mL) was stirred at ambient temperature for 5 h. The resulting precipitate was filtered off and washed with DMF and then diethyl ether. This solid was then taken up in DMF (100 mL), 4A molecular sieves added and the reaction stirred at 80 °C for 3 h. The resulting precipitate was filtered off and washed with diethyl ether to yield the title compound as a white solid.

Mass Spectrum: *167* [MH]+

^{1}H NMR spectrum (DMSO-d_6): 5.11 (2H, s); 7.48 (1H, t); 7.95 (2H, s); 8.49 (1H, s); 8.97 (1H, d).

Step G2: Preparation of *N*-benzyl-*N*-methyl-2-methylaminoimidazo[1,2-*a*]pyridine

A mixture of 2-chloromethylimidazo[1,2-*a*]pyridine (2.00 g, 12.0 mmol), *N*-methylbenzylamine (1.75 g, 14.5 mmol) and powdered K_2CO_3 (3.30 g, 2.40 mmol) in DMF (50 mL) was heated at 90 °C for 4 h. After cooling, the inorganics were filtered off and the filtrate evaporated *in vacuo*. Purification by flash column chromatography (silica gel,

slow gradient, CH_2Cl_2 to 5% MeOH:CH_2Cl_2) gave the title compound as a yellow oil (1.42 g, 48%).

Mass Spectrum: 252 [MH]+

^{1}H NMR spectrum (DMSO-d_6): 2.30 (3H, s); 3.63 (2H, s); 3.79 (2H, s); 6.73 (1H, t); 7.11 (1H, t); 7.20-7.42 (5H, m); 7.55 (1H, s); 7.57 (1H, d); 8.06 (1H,d)

Step G3: Preparation of *N*-benzyl-*N*-methyl-2-methylamino-3-bromoimidazo[1,2-*a*]pyridine

A mixture of *N*-benzyl-*N*-methyl-2-methylaminoimidazo[1,2-*a*]pyridine (1.30 g, 5.20 mmol), poly(4-vinylpyridinium tribromide) (1.82 g, 5.50 mmol) and pyridine (2 drops) in CH_2Cl_2 (20 mL) were stirred at ambient temperature for 16 h. A further portion of poly (4-vinylpyridinium tribromide) (0.400 g, 1.20 mmol) was added and the reaction stirred for a further 16 h. DMF was added, the solid support filtered off, and the mother liquors concentrated *in vacuo*. The residue was triturated with diethyl ether, and filtered to yield the title compound as a cream solid (1.85 g, 99%).

Mass Spectrum: 330, 332 [MH]+

^{1}H NMR spectrum (DMSO-d_6): 2.77 (3H, s); 4.39 (2H, s); 4.43 (2H, br s); 7.16 (1H, t); 7.42-7.50 (4H, m); 7.55-8.00 (2H, m); 7.69 (1H, d); 8.40 (1H, d)

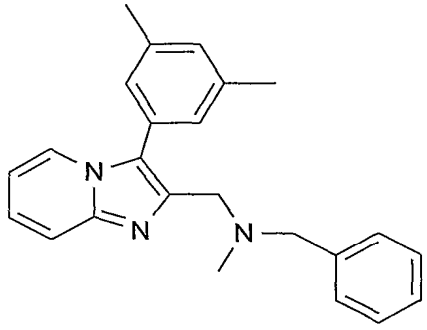
Step G4: Preparation of *N*-benzyl-*N*-methyl-2-methylamino-3-(4-chlorophenyl)imidazo[1,2-*a*]pyridine

To a mixture of *N*-benzyl-*N*-methyl-2-methylamino-3-bromoimidazo[1,2-*a*]pyridine (200 mg, 0.60 mmol), 4-chlorobenzeneboronic acid (141 mg, 0.910 mmol) and saturated Na_2CO_3 (3 mL) in ethanol (1.2 mL) and toluene (6 mL) was added a catalytic amount of $Pd(PPh_3)_4$. The reaction was stirred at 80 °C for 16 h. The reaction was poured onto a hydromatrix column and eluted with CH_2Cl_2. Flash column chromatography (silica gel, slow gradient, neat CH_2Cl_2 to 5% MeOH:CH_2Cl_2) gave an oil. The HCl salt was prepared by addition of 1M HCl in diethyl ether to a solution of the compound in EtOAc to give the title compound as the dihydrochloride as a white solid (26mgs, 10%).

Mass Spectrum: 362 [MH]+

^{1}H NMR spectrum (DMSO-d_6): 2.72 (3H, s); 4.28 (2H, brs); 4.38 (2H, s); 7.18 (1H, t); 7.35-7.41 (3H, m); 7.50-7.57 (2H, m); 7.63 (5H ,s); 7.51 (1H, d); 8.34 (1H,d)

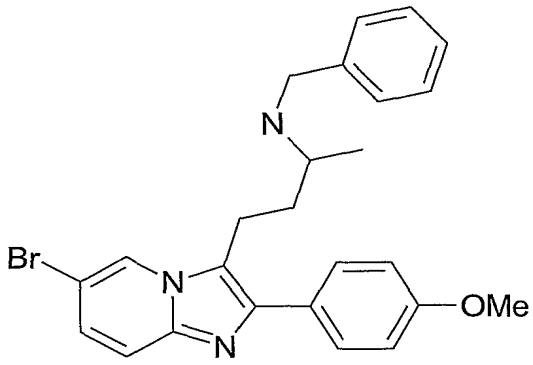
Example H: Preparation of *N*-benzyl-*N*-methyl-2-methylamino-3-(3,5-dimethylphenyl)imidazo[1,2-*a*]pyridine



To a mixture of *N*-benzyl-*N*-methyl-2-methylamino-3-bromoimidazo[1,2-*a*]pyridine (100 mg, 0.400 mmol), 3,5-dimethylbenzene boronic acid (89.0 mg, 0.600 mmol), and sodium carbonate (2 mL) in dioxan (4 mL) was added a catalytic amount of $Pd(PPh_3)_4$. The reaction was stirred at 90 °C for 16 h, then evaporated *in vacuo*. Purification by flash column chromatography (silica gel, slow gradient, neat CH_2Cl_2 to 5% MeOH:CH_2Cl_2) gave an oil. The HCl salt was prepared by addition of 1M HCl in diethyl ether to give the title compound dihydrochloride as a white solid (50.0 mg, 29%).

Mass Spectrum: 356 [MH]+

Example J: Preparation of *N*-Benzyl-5-bromo-3-(3-methylpropylamino)-2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine



Step J1: 5-bromo-2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine

2-amino-5-bromopyridine (5.00 g, 28.9 mmol) was added to a solution of 2-bromo-4-methoxyacetophenone (6.62 g, 28.9 mmol) in DMF (50 mL), and the reaction stirred at 80 °C for 2h. The reaction mixture was partitioned between 1M NaOH (200 mL) and ethyl acetate (200 mL), upon which the majority of the product precipitated from solution and was filtered under vacuum. The organic layer that remained was extracted, dried over magnesium sulfate and evaporated *in vacuo* to give a yellow solid, which was combined with the above to give the title compound (6.74 g, 77%).

^{1}H NMR spectrum (DMSO-d_6): 3.80 (s, 3H); 7.00 (d, 2H); 7.30 (d, 1H); 7.50 (d, 1H); 7.85 (d, 2H); 8.25 (s, 1H); 8.80 (s, 1H).

Mass Spectrum: 303, 305 [MH]+

Step J2: 5-bromo-3-(3-oxo-butyl)-2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine

Methyl vinyl ketone (1.00 mL, 12.0 mmol) was added to a solution of 5-bromo-2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine (1.00 g 3.32 mmol) in glacial acetic acid (30 mL), followed by the addition of acetic anhydride (10 mL). The reaction was stirred at reflux for 14h. The reaction mixture was evaporated *in vacuo* and the crude product purified by flash chromatography (silica gel, eluting from 25% ethyl acetate:hexane to 50% ethyl acetate:hexane) to give the title compound as a yellow solid (1.09 g, 88%).

^{1}H NMR spectrum (DMSO-d_6): 2.10 (s, 3H); 2.85 (t, 2H); 3.10 (t, 2H); 3.80 (s, 3H); 7.00 (d, 2H); 7.25 (d, 1H); 7.50 (d, 1H); 7.65 (d, 2H); 8.70 (s, 1H).

Mass Spectrum: 373, 375 [MH]+

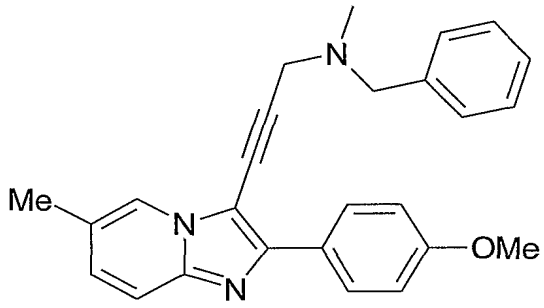
Step J3: *N*-Benzyl-5-bromo-3-(3-methylpropylamino)-2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine

Under an inert atmosphere, benzylamine (0.090 mL, 0.820 mmol) was added to a solution of 5-bromo-3-(3-oxo-butyl)-2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine (300 mg, 0.810 mmol) and toluene sulphonic acid (1 mg, catalytic amount) in anhydrous methanol (10 mL). The reaction mixture was then allowed to reflux over molecular sieves for 16 h. Sodium borohydride (61.0 mg, 1.61 mmol) was added over a period of 30 min, and the reaction left to stir for 30 min. The reaction mixture was evaporated *in vacuo*, and purified by flash chromatography (silica gel, eluting with 1% MeOH: CH_2Cl_2 to 5% MeOH: CH_2Cl_2) to give the title compound as an oil. The hydrochloride salt was formed by addition of HCl in ether, and recrystallised from iso-propanol, to give the title compound hydrochloride as a white solid (40.0 mg, 11%).

^{1}H NMR spectrum (DMSO-d_6): 1.35 (d, 3H); 1.80-2.00 (m, 2H); 2.15-2.25 (m, 2H); 3.75 (q, 1H); 3.85 (s, 3H); 4.00-4.20 (m, 2H); 7.15 (d, 2H); 7.40 (m, 3H); 7.55 (m, 2H); 7.70 (d, 2H); 7.85-8.00 (dd, 2H); 9.20 (s, 1H); 9.45 (s, 1H).

Mass Spectrum: 464, 466 [MH]+

Example K1: Preparation of *N*-Benzyl-*N*-Methyl-5-methyl-3-propargylamino-2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine



Step K1: 5-methyl-2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine

2-amino-5-picoline (5.00 g, 46.3 mmol) was added to a solution of 2-bromo-4-methoxyacetophenone (10.6 g, 46.3 mmol) in DMF (50 mL), and the reaction stirred at 80 °C for 2h. The reaction mixture was partitioned between 1M NaOH (200 mL) and ethyl acetate (200 mL), upon which the majority of the product precipitated from solution and was filtered under vacuum. The organic layer that remained was extracted, dried over magnesium sulfate and evaporated *in vacuo* to give a yellow solid, which was combined with the above to give the title compound (8.20 g, 74%).

^{1}H NMR spectrum (DMSO-d_6): 2.25 (s, 3H); 3.80 (s, 3H); 6.95 (d, 2H); 7.05 (d, 1H); 7.40 (d, 1H); 7.85 (d, 2H); 8.15 (s, 1H); 8.25 (s, 1H).

Mass Spectrum: 239 [MH]+

Step K2: 5-methyl-3-bromo-2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine

Poly(4-vinylpyridinium tribromide) (2.80 g, 8.40 mmol) was added to a solution of 5-methyl-2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine (2.00 g, 8.40 mmol) in dichloromethane, which was followed by the addition of a few drops of pyridine. The reaction was allowed to stir at room temperature for 14h. The reaction mixture was filtered by vacuum, washed with water (2 × 75 mL) and the organics separated, dried over

magnesium sulfate, filtered and evaporated *in vacuo* to give the title compound as a pale yellow solid (1.64 g, 62%).

^{1}H NMR spectrum (DMSO-d_6): 2.25 (s, 3H); 3.80 (s, 3H); 6.95 (d, 2H); 7.05 (d, 1H); 7.40 (d, 1H); 7.85 (d, 2H); 8.15 (s, 1H).

Mass Spectrum: 317, 319 [MH]+

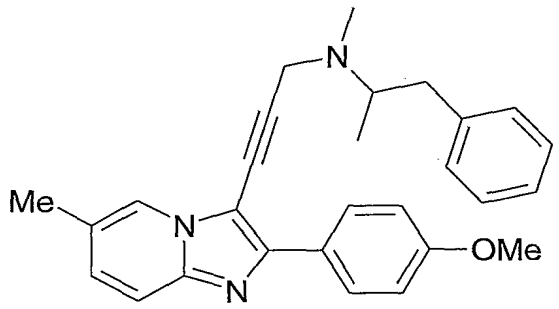
Step K3: *N*-Benzyl-*N*-Methyl-5-methyl-3-propargylamino-2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine

Pargyline hydrochloride (202 mg, 1.26 mmol) was added to a solution of 5-methyl-3-bromo-2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine (20mg, 0.63mmol) in diethylamine (15 mL), and the solution bubbled with nitrogen. Copper Iodide (12.0 mg, 0.060 mmol) was added followed by the addition of bis(triphenylphosphine)palladium dichloride (22.0 mg, 0.030 mmol), and the solution again bubbled with nitrogen. The reaction was then stirred at reflux for 3h, and then at 55 °C for 10 h. The reaction mixture was added to water (50 mL) and extracted with dichloromethane (2 × 50 mL). The organics were dried over magnesium sulfate, filtered, evaporated *in vacuo* and purified by flash chromatography (silica gel, eluting from 10% ethyl acetate:hexane to 40% ethyl acetate:hexane) to give the product and the hydrochloride salt was formed with HCl/ether to give the title compound as an off white solid (37.0 mg, 14%).

^{1}H NMR spectrum ($CDCl_3$): 2.40 (s, 3H); 2.50 (s, 3H); 3.75 (s, 2H); 3.80 (s, 2H); 3.85 (s, 3H); 7.00 (d, 2H); 7.10 (d, 1H); 7.25-7.70 (m, 6H); 8.10 (s, 1H); 8.30 (d, 2H).

Mass Spectrum: 396 [MH]+

Example K2: Preparation of *N*-(*β*-methylphenethyl)-*N*-Methyl-5-methyl-3-propargylamino-2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine

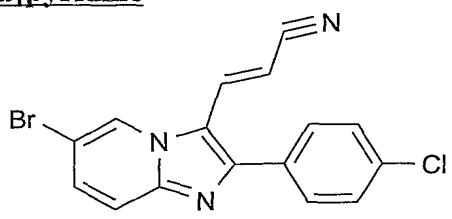


L-Deprenyl (592 mg, 3.16 mmol) was added to a solution of 5-methyl-3-bromo-2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine (500 mg, 1.58 mmol), and the reaction bubbled with nitrogen. Copper iodide (600 mg, 0.320 mmol) and bis(triphenylphosphine)palladium dichloride (110 mg, 0.160 mmol) were added, and the reaction stirred at reflux for 24h. The reaction mixture was partitioned between water (75 mL) and dichloromethane (75 mL), the organics extracted, dried over magnesium sulfate, filtered and evaporated *in vacuo*. The crude product was purified by flash chromatography (silica gel, eluting with 30% EtOAc:Hexane to 80% EtOAc:Hexane) to give an oil. The hydrochloride salt was formed by addition of HCl/ether to give the title compound dihydrochloride as a yellow solid (63mg, 9%).

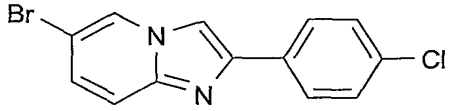
^{1}H NMR spectrum (DMSO-d_6): 1.20 (m, 3H); 2.40 (s, 3H); 2.75 (m, 1H); 2.95 (s, 3H); 3.45 (s, 2H); 3.80 (s, 3H); 4.70 (m, 2H); 7.00 (d, 2H); 7.20-7.65 (m, 7H); 8.20 (d, 2H); 8.70 (s, 1H).

Mass Spectrum: 424 [MH]+

Example L: Preparation of 5-bromo-3-(2*E*-cyanoethenyl)-2-(4-chlorophenyl)imidazo[1,2-*a*]pyridine



Step L1: 5-bromo-2-(4-chlorophenyl)imidazo[1,2-*a*]pyridine



2-amino-5-bromopyridine (3.00 g, 17.3 mmol) was added to a solution of 2-bromo-4-chloroacetophenone (4.02 g, 17.3 mmol) in DMF (30 mL), and the reaction stirred at 80 °C for 2 h. The reaction mixture was partitioned between a 1:1 mixture of water and sodium bicarbonate (200 mL) and ethyl acetate (200 mL), upon which the majority of the product precipitated from solution and was filtered under vacuum. The organic layer that remained was extracted, dried over magnesium sulfate and evaporated *in vacuo* to give an off-white solid, which was combined with the above to give the title compound (2.43 g, 46%).

^{1}H NMR spectrum ($CDCl_3$): 7.10 (d, 2H); 7.40 (m, 1H); 7.50 (d, 1H); 7.80 (s, 1H); 7.85 (d, 2H); 8.25 (s, 1H).

Mass Spectrum: 307, 309 [MH]+

Step L2: 5-bromo-3-formyl-2-(4-chlorophenyl)imidazo[1,2-*a*]pyridine

Under an inert atmosphere, $POCl_3$ (0.200 mL, 2.45 mmol) was added dropwise to DMF (9 mL) - keeping the internal temperature at 10-20 °C. The reaction mixture was warmed to room temperature, which was followed by the slow addition of 5-bromo-2-(4-chlorophenyl)imidazo[1,2-*a*]pyridine (500 mg, 1.64 mmol) as a solid. The reaction was stirred for 12 h at 40 °C. Water was added to the mixture until full precipitation had occurred. The resulting suspension was filtered to give the title compound as a cream solid (440 mg, 81%).

^{1}H NMR spectrum (DMF-d_6): 7.60 (d, 2H); 7.87 (d, 2H); 7.93 (d, 2H); 9.68 (t, 1H); 10.05 (s, 1H).

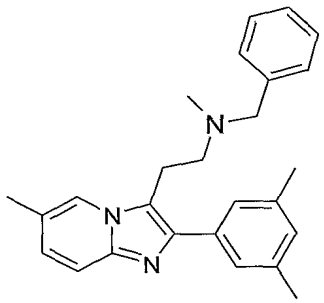
Mass Spectrum: 334, 336 [MH]+

Step L3: 5-bromo-3-(2*E*-cyanoethenyl)-2-(4-chlorophenyl)imidazo[1,2-*a*]pyridine.

At 0 °C, sodium bis(trimethylsilyl)amide (1.0M solution in THF, 1.1 mL, 1.1 mmol) was added to a solution of (cyanomethyl)triphenylphosphoniumchloride (303 mg, 0.900 mmol) in THF, and the reaction allowed to warm to room temperature over 2 h. The reaction was cooled to -78 °C, and 5-bromo-3-formyl-2-(4-chlorophenyl)imidazo[1,2-*a*]pyridine (100 mg, 0.300 mmol) in THF was added dropwise. The reaction was stirred at -78 °C→RT for 14h, and for a further 4h at 40 °C. The reaction mixture was partitioned between water and dichloromethane, the organics separated, dried over magnesium sulfate, filtered and evaporated. The crude product was purified by flash chromatography (silica gel, eluting from 10% ethyl acetate/hexane to 50% ethyl acetate/hexane) to give the title compound as an off-white solid (45.0 mg, 42%).

^{1}H NMR spectrum (DMSO-d_6): 6.15 (d, 1H); 7.50-7.75 (m, 6H); 7.85 (d, 1H); 9.10 (s, 1H)

Example M - Preparation of *N*-Benzyl-*N*-methyl-2-(3,5-dimethylphenyl)-3-ethylamino-5-methylimidazo[1,2-*a*]pyridine.



Step M1: 4-Chloro-2-bromopropyl-3,5-dimethylphenyl ketone.

Pyridinium tribromide (4.56 g 14.3 mmol) was added in one portion to a stirred solution of 4-chloropropyl-3,5-dimethylphenyl ketone (3.00 g 14.3 mmol) [synthesised as described in WO 98/55123] in CH_2Cl_2 (30 mL) at RT and the mixture stirred for 2h. The brown solution was then diluted with ether (200 mL) and washed with 20% NaS_2O_3 (aq) (150 mL), 2M HCl (200 mL) and brine (200 mL). The solution was dried ($MgSO_4$) and concentrated *in vacuo* to give the crude title compound as a brown oil (4.11 g 99%).

Step M2: 2-(3,5-dimethylphenyl)-3-ethylamino-5-methylimidazo[1,2-*a*]pyridine.

A mixture of 2-amino-5-methylpyridine (1.08 g 10.0 mmol) and 4-Chloro-2-bromopropyl-3,5-dimethylphenyl ketone (2.90 g 10.0 mmol) in DMF (15 mL) was heated overnight at 80 °C. The mixture was partitioned EtOAc (50 mL) and saturated $NaHCO_3$ (150mL). The aqueous was extracted with EtOAc (5 × 25 mL) and the combined organics washed with water (25 mL) and brine (25 mL). The solution was dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatograpy (silica gel, slow gradient neat *iso*-hexanes to 50% EtOAc) gave the title compound as a yellow gum (610 mg 20%). HCl salt of title compound was prepared by the addition of 1.0M HCl in diethyl ether to a solution of the

title compound in EtOAc. The salt was precipitated with diethyl ether and collected by centrifuge.

Mass Spectrum: m/e $C_{18}H_{20}ClN_2$ (M+H) 299.16.

^{1}H NMR spectrum ($CDCl_3$): δ ^{1}H NMR (300 MHz) 2.33 - 2.50 (9H, m), 3.50 - 3.65 (2H, t); 3.70 - 3.80 (2H, t); 6.90 - 7.10 (2H, m); 7.36 (2H, s); 7.55 (1H, d); 7.70 - 7.85 (1H, m).

Step M2: *N*-Benzyl-*N*-methyl-2-(3,5-dimethylphenyl)-3-ethylamino-5-methylimidazo[1,2-*a*]pyridine.

N-Methyl-*N*-benzylamine (95 μL 0.737 mmol) was added in one portion to a stirred solution of 2-(3,5-dimethylphenyl)-3-ethylamino-5-methylimidazo[1,2-*a*]pyridine (200 mg 0.670 mmol) and di-isopropylethylamine (128 mL 0.736 mmol) in DMF (25 mL) was heated overnight at 100 °C. The mixture was partitioned EtOAc (2 × 50 mL) and saturated $NaHCO_3$ (250 mL) and the combined organics were dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatograpy (silica gel, slow gradient neat iso-hexanes to 100% EtOAc) gave the title compound as a yellow gum (135 mg 44%). HCl salt of title compound was prepared by the addition of 1.0M HCl in diethyl ether to a solution of the title compound in EtOAc. The salt was precipitated with diethyl ether and collected by centrifuge.

Mass Spectrum: m/e (M+H) 384.67.

^{1}H NMR spectrum (DMSO-d_6 + CD_3COOD): δ ^{1}H NMR (300 MHz) 2.35 (6H, s), 2.75 (3H, s), 3.30 - 3.45 (2H, m); 3.65 - 3.85 (2H, m); 4.20 - 4.50 (2H, m), 7.20 (1H, s); 7.30 (2H, s); 7.35 - 7.45 (3H, m); 7.50 - 7.62 (2H, m); 7.70 - 7.85 (2H, m); 9.05 (1H, s).

THERAPEUTIC USES

Compounds of formulae **I** and **II** are provided as medicaments for antagonising gonadotropin releasing hormone (GnRH) activity in men and women. To this end, a compound of formulae **I** and **II** can be provided as part of a pharmaceutical formulation which also includes a pharmaceutically acceptable diluent or carrier (eg, water). The formulation may be in the form of tablets, capsules, granules, powders, syrups, emulsions (eg, lipid emulsions), suppositories, ointments, creams, drops, suspensions (eg, aqueous or oily suspensions) or solutions (eg, aqueous or oily solutions). If desired, the formulation may include one or more additional substances independently selected from stabilising agents, wetting agents, emulsifying agents, buffers, lactose, sialic acid, magnesium stearate, terra alba, sucrose, corn starch, talc, gelatin, agar, pectin, peanut oil, olive oil, cacao butter and ethylene glycol.

The compound is preferably orally administered to a patient, but other routes of administration are possible, such as parenteral or rectal administration. For intravenous, subcutaneous or intramuscular administration, the patient may receive a daily dose of $0.1 mgkg^{-1}$ to $30 mgkg^{-1}$ (preferably, $5 mgkg^{-1}$ to $20 mgkg^{-1}$) of the compound, the compound being administered 1 to 4 times per day. The intravenous, subcutaneous and intramuscular dose may be given by means of a bolus injection. Alternatively, the intravenous dose may be given by continuous infusion over a period of time. Alternatively, the patient may receive a daily oral dose which is approximately equivalent to the daily parenteral dose, the composition being administered 1 to 4 times per day. A suitable pharmaceutical formulation is one suitable for oral administration in unit dosage form, for example as a tablet or capsule, which contains between 10mg and 1g (preferably, 100 mg and 1g) of the compound of the invention.

The following illustrate representative pharmaceutical dosage forms containing a compound of the invention, or a pharmaceutically acceptable salt or solvate thereof (hereafter referred to as "compound X"), for use in humans.

(a)

Tablet I	mg/tablet
Compound X.	100
Lactose Ph.Eur.	179
Croscarmellose sodium	12.0
Polyvinylpyrrolidone	6
Magnesium stearate	3.0

(b)

Tablet II	mg/tablet
Compound X	50
Lactose Ph.Eur.	229
Croscarmellose sodium	12.0
Polyvinylpyrrolidone	6
Magnesium stearate	3.0

(c)

Tablet III	mg/tablet
Compound X	1.0
Lactose Ph.Eur.	92
Croscarmellose sodium	4.0
Polyvinylpyrrolidone	2.0
Magnesium stearate	1.0

(d)

Capsule	mg/capsule
Compound X	10
Lactose Ph.Eur.	389
Croscarmellose sodium	100
Magnesium stearate	1.

(e)

Injection I	(50 mg/ml)
Compound X	5.0% w/v
Isotonic aqueous solution	to 100%

Buffers, pharmaceutically acceptable cosolvents (eg, polyethylene glycol, propylene glycol, glycerol or EtOH) or complexing agents such as hydroxy-propyl β cyclodextrin may be used to aid formulation.

One aspect of the invention relates to the use of compounds according to the invention for reducing the secretion of LH and/or FSH by the pituitary gland of a patient. In this respect, the reduction may be by way of a reduction in biosynthesis of the LH and FSH and/or a reduction in the release of LH and FSH by the pituitary gland. Thus, compounds according to the invention can be used for therapeutically treating and/or preventing a sex hormone related condition in the patient. By "preventing" we mean reducing the patient's risk of contracting the condition. By "treating" we mean eradicating the condition or reducing its severity in the patient. Examples of sex hormone related conditions are: a sex hormone dependent cancer, benign prostatic hypertrophy, myoma of the uterus, endometriosis, polycystic ovarian disease, uterine fibroids, prostatauxe, myoma uteri, hirsutism and precocious puberty. Examples of sex hormone dependent cancers are: prostatic cancer, uterine cancer, breast cancer and pituitary gonadotrophe adenoma.

ASSAYS

The ability of compounds according to the invention to act as antagonists of GnRH can be determined using the following *in vitro* assays.

Binding Assay Using Rat pituitary GnRH Receptor

The assay is performed as follows:-

1. Incubate crude plasma membranes prepared from rat pituitary tissues in a Tris.HCl buffer (pH. 7.5, 50 mM) containing bovine serum albumin (0.1%), [I-125]D-t-Bu-Ser6-Pro9-ethyl amide-GnRH, and the test compound. Incubation is at 4°C for 90 minutes to 2 hours.

2. Rapidly filter and repeatedly wash through a glass fibre filter.

3. Determine the radioactivity of membrane bound radio-ligands using a gamma counter.

From this data, the IC_{50} of the test compound can be determined as the concentration of the compound required to inhibit radio-ligand binding to GnRH receptors by 50%.

Binding Assay Using Human GnRH Receptor

Crude membranes prepared from CHO cells expressing human GnRH receptors are sources for the GnRH receptor. The binding activity of compounds according to the invention can be determined as an IC_{50} which is the compound concentration required to inhibit the specific binding of [^{125}I]buserelin to GnRH receptors by 50%. [^{125}I]Buserelin (a peptide GnRH analogue) is used here as a radiolabelled ligand of the receptor.

Assay to Determine Inhibition of LH release

The LH release assay can be used to demonstrate antagonist activity of compounds, as demonstrated by a reduction in GnRH-induced LH release.

Preparation of Pituitary Glands

Pituitary glands obtained from rats are prepared as follows. Suitable rats are Wistar male rats (150-200g) which have been maintained at a constant temperature (eg, 25°C) on a 12 hour light/12 hour dark cycle. The rats are sacrificed by decapitation before the pituitary glands are aseptically removed to tube containing Hank's Balanced Salt Solution (HBSS). The glands are further processed by:-

1. Centrifugation at 250 x g for 5 minutes;
2. Aspiration of the HBSS solution;
3. Transfer of the glands to a petri dish before mincing with a scalpel;
4. Transfer of the minced tissue to a centrifuge tube by suspending the tissue three successive times in 10 ml aliquots of HBSS containing 0.2% collagenase and 0.2% hyaluronidase;
5. Cell dispersion by gentle stirring of the tissue suspension while the tube is kept in a water bath at 37°C;
6. Aspiration 20 to 30 times using a pipette, undigested pituitary fragments being allowed to settle for 3 to 5 minutes;
7. Aspiration of the suspended cells followed by centrifugation at 1200 x g for 5 minutes;
8. Resuspension of the cells in culture medium of DMEM containing 0.37% $NaHCO_3$, 10% horse serum, 2.5% foetal bovine serum, 1% non essential amino acids, 1% glutamine and 0.1% gentamycin;

9. Treatment of the undigested pituitary fragments 3 times with 30 ml aliquots of the collagenase and hyaluronidase;
10. Pooling of the cell suspensions and dilution to a concentration of 3 x 10^5 cells/ml;
11. Placing of 1.0ml of this suspension in each of a 24 well tray, with the cells being maintained in a humidified 5% CO_2/95% air atmosphere at 37°C for 3 to 4 days

Testing of Compounds

The test compound is dissolved in DMSO to a final concentration of 0.5% in the incubation medium.

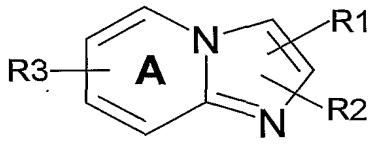
1.5 hours prior to the assay, the cells are washed three times with DMEM containing 0.37% $NaHCO_3$, 10% horse serum, 2.5% foetal bovine serum, 1% non essential amino acids (100X), 1% glutamine (100X), 1% penicillin/streptomycin (10,000 units of each per ml) and 25 mM HEPES at pH 7.4. Immediately prior to the assay, the cells are again washed twice in this medium .

Following this, 1ml of fresh medium containing the test compound and 2nM GnRH is added to two wells. For other test compounds (where it is desired to test more than one compound), these are added to other respective duplicate wells. Incubation is then carried out at 37°C for three hours.

Following incubation, each well is analysed by removing the medium from the well and centrifuging the medium at 2000 x g for 15 minutes to remove any cellular material. The supernatant is removed and assayed for LH content using a double antibody radio-immuno assay. Comparison with a suitable control (no test compound) is used to determine whether the test compound reduces LH release. Compounds according to the present invention have activity at a concentration from 1nM to 30 μM.

CLAIMS

1. A compound of formula **I** or a pharmaceutically acceptable salt or solvate thereof

I 

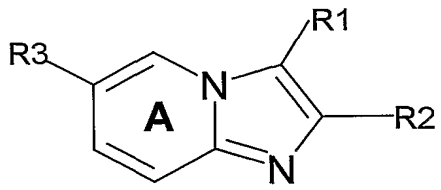
wherein:-

R1 and R2 are independently selected from hydrogen and a group bonded through a carbon atom, a nitrogen atom, an oxygen atom or a sulphur atom;

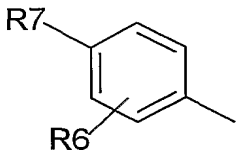
R3 is selected from $(CH_2)_a$-R4, wherein R4 represents an optionally substituted C6 to C14 aryl or an optionally substituted homo- or bi-cyclic heterocyclic ring and a represents zero or an integer from 1 to 5; a group bonded through a heteroatom; an optionally substituted C1 to C20 hydrocarbon residue; optionally substituted C1 to C6 alkyl; C1 to C6 alkyl substituted with a group bonded through a sulphur atom; OR5, wherein R5 represents H or C1 to C6 alkyl; a carbonyl group optionally substituted with a hydrocarbon residue, the residue being optionally substituted; an esterified or amidated carboxyl group; hydrogen; optionally substituted aralkyl; optionally substituted cycloalkyl; and a group of formula W-$(CH_2)_d$, wherein d represents zero or an integer from 1 to 5 and W represents aryl having an optional substitutent selected from halogen, nitro, cyano, amino, an optionally substituted carboxyl, alkylenedioxy wherein the alkylene is C1 to C6, and a group of formula –X-R', wherein X represents a chemical bond or a spacer group and R' represents an optionally substituted cycloalkyl or an optionally substituted heterocyclic group;

and ring **A** is optionally further substituted.

2. The compound of formula **II** or a pharmaceutically acceptable salt or solvate thereof, wherein R1, R2 and R3 are as defined in claim 1

II 

3. The compound of claim 1 or 2, wherein R4 represents a group of the formula:-



wherein:-

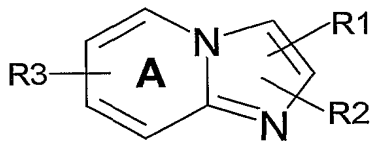
R6 is selected from hydrogen; halogen; and a group bonded through a carbon atom, a nitrogen atom, an oxygen atom or a sulphur atom; and

R7 is selected from hydrogen; halogen; nitro; cyano; and a hydrocarbon residue optionally substituted by a group bonded through an oxygen atom, a nitrogen atom or a sulphur atom.

4. The compound of any preceding claim, wherein R1 and R2 are independently selected from a group of the formula R8-$(CH_2)_b$-, wherein each b independently represents zero or an integer from 1 to 5 and each R8 represents a group bonded through a nitrogen atom; a group of of the formula R9-B'-, wherein R9 is an optionally substituted phenyl and B' is a chemical bond or spacer group; R10-$(CH_2)_c$-, wherein R10 is an optionally substituted amino and c is zero or an integer from 1 to 5; an optionally substituted C6 to C14 aryl; an optionally substituted C1 to C20 hydrocarbon residue; and optionally substituted C1 to C6 alkyl.

5. A compound of formula **Ia** or a pharmaceutically acceptable salt or solvate thereof, wherein

Ia



wherein:-

R1 and R2 are independently selected from hydrogen and a group bonded through a carbon atom, a nitrogen atom, an oxygen atom or a sulphur atom;

R3 represents hydrogen; optionally substituted C1 to C6 alkyl; optionally substituted aryl; C1 to C3 perfluoroalkyl; CN; NO_2; halogen; or $R11O(CH_2)_e$ -;

wherein R11 represents hydrogen; optionally substituted C1 to C6 alkyl; optionally substituted aryl; optionally substituted aralkyl; an optionally substituted carbocyclic ring of 3-7 atoms; or a mono- or bi-cyclic heterocyclic ring comprising from 1 to 4 heteroatoms selected from O, N and S and being optionally substituted by R12, R13 and R14, or being optionally substituted by C1 to C6 alkyl substituted by a mono- or bi-cyclic heterocyclic ring comprising from 1 to 4 heteroatoms selected from O, N and S and which ring is optionally substituted by R12, R13 and R14;

For R12, R13 and R14, either:-

(a) R12, R13 and R14 independently represent hydrogen; optionally substituted C1 to C6 alkyl; optionally substituted C2 to C6 alkenyl; CN; nitro; C1 to C3 perfluoroalkyl; C1 to C3 perfluoroalkoxy; optionally substituted aryl; optionally substituted aralkyl; $(CH_2)_fS(O)_gR15$; or halogen; or

(b) R12 meets the definition in (a) and R13 and R14 together represent a 3C to 7C carbocyclic ring or a heterocyclic ring comprising from 1 to 3 heteroatoms selected from O, N and S;

R15 represents hydrogen; optionally substituted C1 to C6 alkyl; C1 to C3 perfluoroalkyl; or optionally substituted aryl;

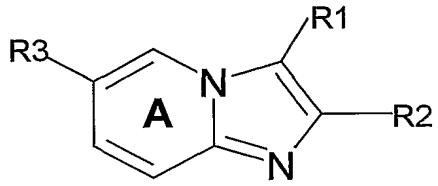
e and f independently represent 0, 1, 2, 3, 4 or 5; and

g represents 0, 1 or 2.

and ring **A** is optionally further substituted.

6. The compound of formula **IIa** or a pharmaceutically acceptable salt or solvate thereof, wherein R1, R2 and R3 are as defined in claim 5

IIa



7. The compound of claim 5 or 6, wherein ring **A** has a further substituent selected from halogen and –Q(R16)R17, wherein:-

Q represents N; O; $S(O)_h$; C(O); $(CR18R19)_i$; a single bond to R16; optionally substituted C2 to C6 alkenyl; or optionally substituted C2 to C6 alkynyl; with the proviso that when Q is O; $S(O)_h$; C(O); $(CR18R19)_i$; or a single bond, R17 is absent; and

For R16 and R17, either:-

(c) R16 represents hydrogen or optionally substituted C1 to C6 alkyl; and R17 represents hydrogen; C(O)NR18R19; C(O)R20; NR18R19; C(O)R18; NR19C(O)R18; NR19C(O)NR18R19; $NR19S(O)_2R18$; $NR19S(O)_2NR18R19$;

OC(O)R18; OC(O)NR18R19; OR18; $S(O)_jR18$; $S(O)_jNR18R19$; a mono- or bi-cyclic heterocyclic ring comprising from 1 to 4 heteroatoms selected from O, N and S and being optionally substituted by R21, R22 and R23, or being optionally substituted by an optionally substituted C1 to C6 alkyl; or

(d) the structure –Q(R16)R17 represents a heterocyclic ring comprising one or more heteroatoms selected from O, N and S and optionally substituted by R21, R22 and R23; or

(e) the structure –Q(R16)R17 represents a 3-7 membered carbocyclic ring or =O;

For R18 and R19, either:-

(f) Each R18 and R19 independently represents a bond; hydrogen; optionally substituted C1 to C6 alkyl; optionally substituted aryl; optionally substituted aralkyl; an optionally substituted carbocyclic ring of 3-7 atoms; or a mono- or bi-cyclic heterocyclic ring comprising from 1 to 4 heteroatoms selected from O, N and S and being optionally substituted by R21, R22 and R23, or being optionally substituted by C1 to C6 alkyl substituted by a mono- or bi-cyclic heterocyclic ring comprising from 1 to 4 heteroatoms selected from O, N and S and which ring is optionally substituted by R21, R22 and R23; or

(g) R18 and R19 together form part of an optionally substituted 3 to 9-membered ring;

R20 represents hydrogen; optionally substituted C1 to C6 alkyl; optionally substituted aryl; or optionally substituted aralkyl;

For R21, R22 and R23, either:-

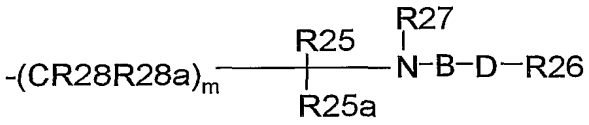
(h) Each R21, R22 and R23 independently represents hydrogen; optionally substituted C1 to C6 alkyl; optionally substituted C2 to C6 alkenyl; CN; nitro; C1 to C3 perfluoroalkyl; C1 to C3 perfluoroalkoxy; optionally substituted aryl; optionally substituted aralkyl; $R18O(CH_2)_k$, where R18 meets the definition in section (f); $(CH_2)_kS(O)_lR24$; or halogen; or

(i) R21 is as defined in section (h) and R22 and R23 together represent a C3 to C7 carbocyclic ring or a heterocyclic ring containing from 1 to 3 heteroatoms selected from O, N and S;

R24 represents hydrogen; optionally substituted C1 to C6 alkyl; C1 to C3 perfluoroalkyl; or optionally substituted aryl;

i and k independently represent 0, 1, 2, 3, 4 or 5; and
each h, j and l independently represent 0, 1 or 2.

8. The compound of claim 1, 2, 3, 5, 6 or 7, wherein R1 represents the group



wherein:-
B represents R29-Y-R29, wherein Y represents optionally substituted aryl;

D is selected from a bond; -OR29-; -C(=O)R29-; -$S(O)_n$R29-; -NR29R30-; -OC(=O)R29-; -C(=O)OR29-; -NR31C(=O)R29-; -C(=O)NR31R29-; -$OS(O)_n$R29-; -$S(O)_n$OR29-; and –$NR31S(O)_n$R29-;

For R25, R25a, R27, R28 and R28a either:-
(i) R25, R25a, R27, R28 and R28a are independently selected from hydrogen; optionally substituted C1 to C6 alkyl; optionally substituted aryl; and optionally substituted aralkyl;

(j) R25 and R25a together represent a 3-7 membered carbocyclic ring or =O; and R27, R28 and R28a meet the definition in section (i);

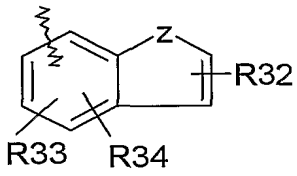
(k)R25, R25a and R27 meet the definition in section (i); and R28 and R28a together represent a 3-7 membered carbocyclic ring or =O;

(l) R25 and R28 together represent a heterocyclic ring comprising from 3 to 7 carbon atoms and at least one heteroatom; and R25a, R27 and R28a meet the definition in section (i);

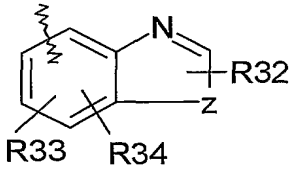
(m) R27 and R28 together represent a heterocyclic ring comprising from 3 to 7 carbon atoms and at least one heteroatom; and R25, R25a and R28a meet the definition in section (i); or

(n)R25 and R27 together represent a heterocyclic ring comprising from 3 to 7 carbon atoms and at least one heteroatom; and R25a, R28 and R28a meet the definition in section (i);

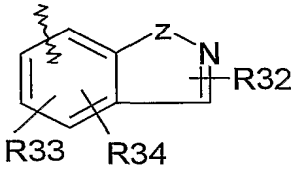
R26 represents a substituent selected from **III** to **XXIX** or an N-oxide thereof:-



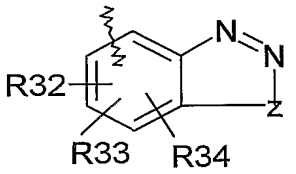
III



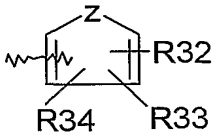
IV



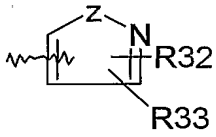
V



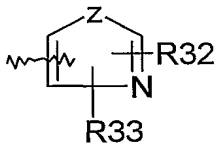
VI



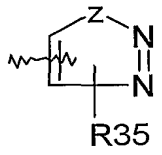
VII



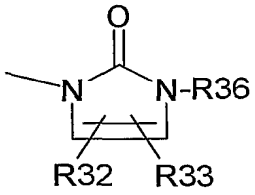
VIII



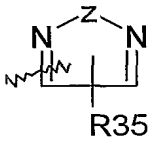
IX



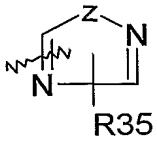
X



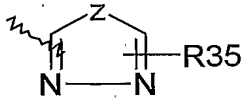
XI



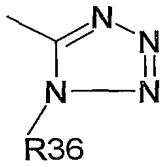
XII



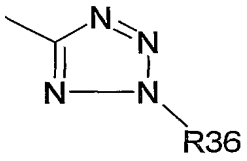
XIII



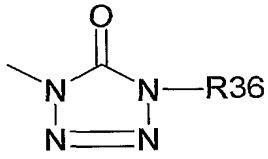
XIV



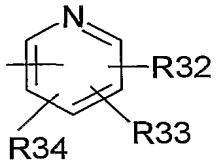
XV



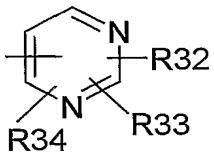
XVI



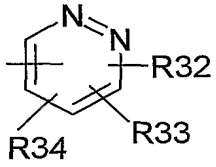
XVII



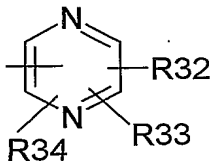
XVIII



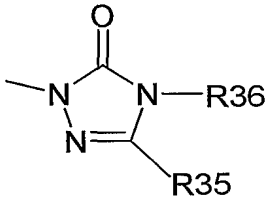
XIX



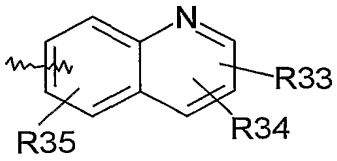
XX



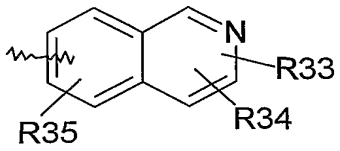
XXI



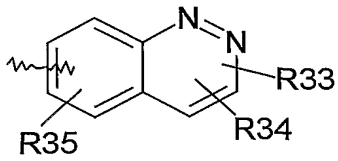
XXII



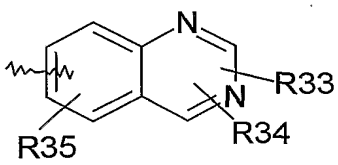
XXIII



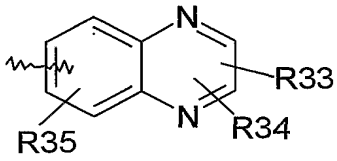
XXIV



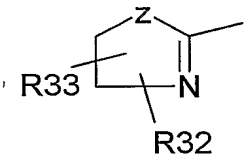
XXV



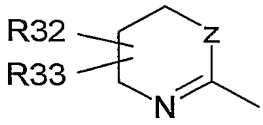
XXVI



XXVII



XXVIII



XXIX

Each R29 is independently selected from a bond and optionally substituted C1 to C4 alkyl;

R30 represents hydrogen; optionally substituted C1 to C6 alkyl; C(O)OR37; $C(O)N(R37)_2$; C(O)R37; or $S(O)_oR37$;

R31 and R36 independently represent hydrogen; optionally substituted C1 to C6 alkyl; optionally substituted aryl; optionally substituted aralkyl; an optionally substituted carbocyclic ring of 3-7 atoms; or a mono- or bi-cyclic heterocyclic ring comprising from 1 to 4 heteroatoms selected from O, N and S and being optionally substituted by R38, R39 and R40, or being optionally substituted by C1 to C6 alkyl substituted by a mono- or bi-cyclic heterocyclic ring comprising from 1 to 4 heteroatoms selected from O, N and S and which ring is optionally substituted by R38, R39 and R40;

R32 represents hydrogen; OH; NR41R42; $NR37SO_2$(optionally substituted C1 to C6 alkyl); $NR37SO_2$(optionally substituted aryl); $NR37SO_2$(C1 to C3 perfluoroalkyl); SO_2NR37(optionally substituted C1 to C6 alkyl); SO_2NR37(optionally substituted aryl); SO_2NR37(C1 to C3 perfluoroalkyl); SO_2NR37(C(O)-optionally substituted C1 to C6 alkyl); SO_2NR37(C(O)-optionally substituted aryl); $S(O)_p$(optionally substituted C1 to C6 alkyl); $S(O)_p$(optionally substituted aryl); C1 to C3 perfluoroalkyl; C1 to C3 perfluoroalkoxy; optionally substituted C1 to C6 alkoxy; COOH; halogen; NO_2; or CN;

R33 and R34 are independently selected from hydrogen; optionally substituted C1 to C6 alkyl; optionally substituted C2 to C6 alkenyl; CN; nitro; C1 to C3 perfluoroalkyl; C1 to C3 perfluoroalkoxy; optionally substituted aryl; optionally substituted aralkyl; $R37O(CH_2)_q$-; $R37C(O)O(CH_2)_q$-;

R37OC(O)$(CH_2)_q$-; -$(CH_2)_q$S(O)$_r$R', where R' is hydrogen, optionally substituted C1 to C6 alkyl, C1 to C3 perfluoroalkyl or optionally substituted aryl; -$(CH_2)_q$C(O)N(R37)$_2$; or halogen;

R35 meets a definition of either R32 or R33;

Each R37 independently represents hydrogen; optionally substituted C1 to C6 alkyl; optionally substituted aryl; optionally substituted aralkyl; or an optionally substituted 3 to 7-membered carbocyclic ring;

R38, R39 and R40 independently represent hydrogen; optionally substituted C1 to C6 alkyl; optionally substituted C2 to C6 alkenyl; CN; nitro; C1 to C3 perfluoroalkyl; C1 to C3 perfluoroalkoxy; optionally substituted aryl; optionally substituted aralkyl; $(CH_2)_s$S(O)$_t$R43; or halogen;

For R41 and R42, either:-

(o)R41 represents hydrogen or optionally substituted C1 to C6 alkyl; and R42 represents hydrogen; C(O)NR18'R19'; C(O)R20'; NR18'R19'; C(O)R18'; NR19'C(O)R18'; NR19'C(O)NR18'R19'; NR19'S(O)$_2$R18'; NR19'S(O)$_2$NR18'R19'; OC(O)R18'; OC(O)NR18'R19'; OR18'; S(O)$_u$R18'; S(O)$_u$NR18'R19'; a mono- or bi-cyclic heterocyclic ring comprising from 1 to 4 heteroatoms selected from O, N and S and being optionally substituted by R21', R22' and R23', or being optionally substituted by an optionally substituted C1 to C6 alkyl; wherein R18', R19', R20', R21', R22' and R23' meet a definition respectively of R18, R19, R20, R21, R22 and R23 in claim 7; or

(p) the structure –N(R41)R42 represents a heterocyclic ring comprising one or more heteroatoms selected from O, N and S and optionally substituted by R21', R22' and R23'; wherein R21', R22' and R23' meet a definition respectively of R21, R22 and R23 in claim 7;

R43 represents hydrogen; optionally substituted C1 to C6 alkyl; C1 to C3 perfluoroalkyl; or optionally substituted aryl;

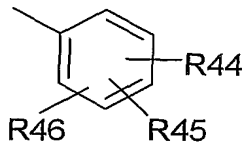
Z represents O, S or NR18';

R18' meets a definition of R18 in section (f) of claim 7;

Each m, q and s independently represent 0, 1, 2, 3, 4 or 5; and

n, o, p, r, t and u independently represent 0, 1 or 2.

9. The compound of any one of claims 1 to 3, 5, 6, 7 and 8, wherein R2 represents a substituent of formula **XXX**:-



XXX

R44, R45 and R46 independently represent hydrogen; optionally substituted C1 to C6 alkyl; optionally substituted C2 to C6 alkenyl; CN; nitro; C1 to C3 perfluoroalkyl; C1 to C3 perfluoroalkoxy; optionally substituted aryl; optionally substituted aralkyl; $(CH_2)_vS(O)_wR47$; or halogen;

R47 represents hydrogen; optionally substituted C1 to C6 alkyl; C1 to C3 perfluoroalkyl; or optionally substituted aryl;

v represents 0, 1, 2, 3, 4 or 5; and

w represents 0, 1 or 2.

10. The compound of claim 1, wherein the compound is selected from

2-{2-(3,5-Dimethyl-phenyl)-3-[2-(4-pyridin-4-yl-butylamino)-ethyl]-imidazo[1,2-a]pyridin-6-yl}-N,N-diisobutyl-isobutyramide;

2-(3,5-Dimethyl-phenyl)-3-{2-[(5-pyridin-3-yl-thiophen-2-ylmethyl)-amino]-ethyl}-imidazo[1,2-a]pyridine-6-carboxylic acid diisopropylamide;

1-(7-Aza-bicyclo[2.2.1]hept-7-yl)-2-{2-(3,5-dimethyl-phenyl)-3-[2-(4-pyridin-3-yl-benzylamino)-ethyl]-imidazo[1,2-a]pyridin-6-yl}-2-methyl-propan-1-one;

1-(7-Aza-bicyclo[2.2.1]hept-7-yl)-2-{2-(3,5-dimethyl-phenyl)-3-[2-(4-pyridin-4-yl-benzylamino)-ethyl]-imidazo[1,2-a]pyridin-6-yl}-2-methyl-propan-1-one;

1-(7-Aza-bicylco[2.2.1]hept-7-yl)-2-(2-(3,5-dimethyl-phenyl)-3-{(R)-1-methyl-2-[2-(3-methyl-3*H*-imidazo[4,5-*b*]pyridin-6-yl)-ethylamino]-ethyl}-imidazo[1,2-*a*]pyridin-6-yl)-2-methyl-propan-1-one;

2-(2-(3,5-dimethyl-phenyl)-3-{(R)-2-[2-(4-methanesulfonylamino-phenyl)-ethylamino]-1-methyl-ethyl}-imidazo[1,2-*a*]pyridin-6-yl)-*N*,*N*-diisobutyl-isobutyramide;

2-{2-(3,5-dimethyl-phenyl)-3-[2-(4-pyridin-4-yl-butylamino)-ethyl]-imidazo[1,2-*a*]pyridin-6-yl}-*N*,*N*-diethyl-isobutyramide;

2-(3,5-dimethyl-phenyl)-3-[2-(4-pyridin-4-yl-butylamino)-ethyl]-imidazo[1,2-*a*]pyridine-6-carboxylic acid diethylamide;

Benzyl-[2-(4-methoxyphenyl)-6-oxazol-4-yl-imidazo[1,2-a]pyridin-3-ylmethyl]-methylamine;

Propane-2-sulfonic acid 3-[(benzylmethylamino)-methyl]-2-[4-(2-methyl-propanoylamino)-phenyl]-imidazo[1,2-a]pyridin-6-yl ester;

3-[(Benzylmethylamino)-methyl]-2-(4-methoxyphenyl)-imidazo[1,2-a]pyridine-6-carboxylic acid ethyl ester;

2-(4-Acetylaminophenyl)-3-[(benzylmethylamino)-methyl]-imidazo[1,2-a]pyridine-6-carboxylic acid ethyl ester;

N-{4-[3-(Benzylmethylamino)-methyl]-6-(2-methylpropanoyl)-imidazo[1,2-a]pyridin-2-yl]-phenyl}-isobutyramide;

N-{4-[3-(Benzylmethylamino)-methyl]-6-(1-phenylmethanoyl)-imidazo[1,2-a]pyridin-2-yl]-phenyl}-isobutyramide;

3-[(Benzylmethylamino)-methyl]-2-[4-(2-methyl-propanoylamino)-phenyl]-imidazo[1,2-a]pyridine-6-carboxylic acid isopropyl ester;

3-[(Benzylmethylamino)-methyl]-2-[4-(3-methylureido)-phenyl]-imidazo[1,2-a]pyridine-6-carboxylic acid benzylmethylamide;

3-[(Benzylmethylamino)-methyl]-2-[4-(3-methylureido)-phenyl]-imidazo[1,2-a]pyridine-6-carboxylic acid isopropylamide; or

3-[(Benzylmethylamino)-methyl]-2-[4-(3-methylureido)-phenyl]-imidazo[1,2-a]pyridine-6-carboxylic acid isopropylmethylamide;

or a pharmaceutically acceptable salt or solvate thereof.

11. A compound according to any preceding claim for use as a medicament.

12. A pharmaceutical formulation comprising a compound according to any one of claims 1 to 10 and a pharmaceutically acceptable diluent or carrier.

13. Use of a compound according to any one of claims 1 to 10, in the manufacture of a composition, for antagonising gonadotropin releasing hormone activity.

14. Use of a compound according to any one of claims 1 to 10, in the manufacture of a medicament for administration to a patient, for reducing the secretion of luteinising hormone by the pituitary gland of the patient.

15. Use of a compound according to any one of claims 1 to 10, in the manufacture of a medicament for administration to a patient, for therapeutically treating and/or preventing a sex hormone related condition in the patient.

16. The use according to claim 15, wherein the sex hormone related condition is selected from a sex hormone dependent cancer, benign prostatic hypertrophy or myoma of the uterus.

17. The use according to claim 16, wherein the sex hormone dependent cancer is selected from prostatic cancer, uterine cancer, breast cancer and pituitary gonadotrophe adenoma.

18. A method of antagonising gonadotropin releasing hormone activity in a patient, comprising administering to the patient a compound according to any one of claims 1 to 10.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
29 August 2002 (29.08.2002)

PCT

(10) International Publication Number
WO 02/066477 A3

(51) International Patent Classification[7]: C07D 471/04, A61K 31/437, A61P 5/00, 5/00 // (C07D 471/04, 235:00, 221:00)

(21) International Application Number: PCT/GB02/00634

(22) International Filing Date: 15 February 2002 (15.02.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0100567-7 20 February 2001 (20.02.2001) SE

(71) Applicant *(for AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, SZ, BE, CY, FR, GR, IE, IT, MC, NL, BF only)*: **ASTRAZENECA AB** [SE/SE]; Sodertalje, S- 151 85 (SE).

(71) Applicant *(for MG only)*: **ASTRAZENECA UK LIMITED** [GB/GB]; 15 Stanhope Gate, London, Greater London W1Y 6LN (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **DOSSETTER, Alexander, Graham** [GB/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). **KENNY, Peter** [GB/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). **MCKERRECHER, Darren** [GB/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). **WARDLEWORTH, Michael** [GB/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).

(74) Agent: **BRYANT, Tracey, et al**; Astrazeneca, Global Intellectual Property, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:
— *of inventorship (Rule 4.17(iv)) for US only*

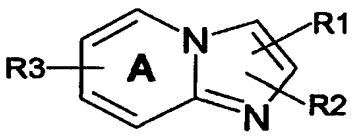
Published:
— *with international search report*

(88) Date of publication of the international search report:
17 October 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/066477 A3

(54) Title: IMIDAZOPYRIDINES



(I)

(57) Abstract: The present invention relates to compounds of formula I which are antagonists of gonadotropin releasing hormone (GnRH) activity. The invention also relates to pharmaceutical formulations, the use of a compound of the present invention in the manufacture of a medicament, a method of therapeutic treatment using such a compound and processes for producing the compounds wherein: - R1, R2 and R3 are as defined in the description; and ring A is optionally further substituted.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 02/00634

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D471/04 A61K31/437 A61P5/00 A61P35/00
//(C07D471/04,235:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 41252 A (MERCK) 19 August 1999 (1999-08-19) claims 1-7; examples 1G,1I	1,12-17
X	WO 99 41251 A (MERCK) 19 August 1999 (1999-08-19) claims 1-7; examples 1Q,1S,1U,1W,	1,12-17
X	WO 99 20223 A (NOVONORDISK) 29 April 1999 (1999-04-29) claims 1, 3 and 8 (E 1020)	1,12,14, 15
X	WO 98 03505 A (TAKEDA) 29 January 1998 (1998-01-29) page 134; claims 1,13,14; examples 120,136	1,12,17

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 July 2002	26/07/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Alfaro Faus, I

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 02/00634

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 19953 A (ASTA MEDICA) 5 June 1997 (1997-06-05) claims 1,17; example 28	1,12, 14-17
P,X	WO 01 55119 A (NEUROCRINE) 2 August 2001 (2001-08-02) page 132 -page 134; claims 1,39-42; example 12	1,12,13, 15-17
P,X	WO 01 83481 A (IMP CANCER RES TECHNOLOGY) 8 November 2001 (2001-11-08) abstract page 29 -page 43	1,12,16
X	KAMINSKI J J ET AL: "JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 28, no. 7, 1985, pages 876-892, XP002094814 ISSN: 0022-2623 tables 3,4	1,12

INTERNATIONAL SEARCH REPORT

tional application No.
PCT/GB 02/00634

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 18 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1-12 (all partially)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-12 (all partially)

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claim(s) is impossible. Consequently, the search is only complete for the use of the compounds of claim 1 according to claims 13 to 18

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 02/00634

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9941252	A	19-08-1999	AU	2597899 A	30-08-1999
			CA	2318957 A1	19-08-1999
			EP	1062215 A1	27-12-2000
			JP	2002503661 T	05-02-2002
			WO	9941252 A1	19-08-1999
WO 9941251	A	19-08-1999	AU	2597299 A	30-08-1999
			CA	2317451 A1	19-08-1999
			EP	1068195 A1	17-01-2001
			JP	2002503660 T	05-02-2002
			WO	9941251 A1	19-08-1999
			US	6159975 A	12-12-2000
WO 9920223	A	29-04-1999	AU	9621598 A	10-05-1999
			WO	9920223 A2	29-04-1999
			EP	1028690 A2	23-08-2000
			US	6297243 B1	02-10-2001
WO 9803505	A	29-01-1998	AU	3461697 A	10-02-1998
			CN	1349990 A	22-05-2002
			CN	1223653 A ,B	21-07-1999
			EP	0912562 A1	06-05-1999
			WO	9803505 A2	29-01-1998
			JP	11060571 A	02-03-1999
			US	6211215 B1	03-04-2001
			ZA	9706378 A	19-01-1999
WO 9719953	A	05-06-1997	DE	19544212 A1	05-06-1997
			AU	706546 B2	17-06-1999
			AU	1867097 A	19-06-1997
			BG	102514 A	30-04-1999
			BR	9611760 A	05-10-1999
			CA	2238570 A1	05-06-1997
			CN	1202882 A	23-12-1998
			CZ	9801358 A3	16-09-1998
			WO	9719953 A2	05-06-1997
			EE	9800165 A	15-12-1998
			EP	0876337 A2	11-11-1998
			HU	9901656 A2	30-08-1999
			JP	2000501083 T	02-02-2000
			NO	982366 A	25-05-1998
			NZ	330521 A	28-01-1999
			PL	326977 A1	09-11-1998
			RU	2163910 C2	10-03-2001
			SK	62998 A3	12-07-1999
			US	5942493 A	24-08-1999
			ZA	9609987 A	17-06-1997
WO 0155119	A	02-08-2001	AU	3797501 A	07-08-2001
			WO	0155119 A2	02-08-2001
WO 0183481	A	08-11-2001	AU	5260901 A	12-11-2001
			WO	0183481 A1	08-11-2001